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ANNALS OF INTERNAL MEDICINE

VOLUME 35 NOVEMBER, 1951 NUMBER 5

ENDOCRINE PATTERNS DURING AGING *

By THOMAS HODGE MCGAVACK, M.D., F.A.C.P., *New York, N. Y.*

AGING may be conceived as having two major phases: one, of evolution, growth and development; the other, of involution, degeneration and senescence. Our present concern is with the latter. Involutionary changes do not begin at any specific or given age, but proceed in more or less orderly fashion into senescence and death. Minot [1] looked upon senescence as the natural result and end of the growth process. It is difficult to determine which processes in the aging individual result from heredity, which from the passage of years and which from the various stresses that are encountered throughout life. The menopause in woman affords a rather sharply defined point at which involutional alterations may be thought to take precedence over those of an evolutional or developmental type. There is no such event in man to enable one to divide readily one set of processes from the other. Nevertheless, as G. Stanley Hall phrased it, during "the last half of life" man is subjected to alterations which are of a predominantly involutionary type and lead to senescence.

Not only some of the functional but also many of the histologic changes which develop during aging are, at least partially, reversible under the influence of specific therapy,[2] as, for instance, the response of "old" thyroid glands to thyrotrophin (TSH),[3] cornification of the vaginal mucosa by estrogen; the reconversion of the hyaline-fibrous tissue of the uterine mucosa and muscle to fibrillar-cellular tissue under the influence of estrogen,[5] and the increase in eosinophils in the anterior pituitary following the administration of testosterone or estrogen.[4]

I. HISTOLOGIC CHANGES IN AGING ENDOCRINE GLANDS AND SOME HORMONAL INFLUENCES AFFECTING THEM

Histologic changes in the endocrine glands during aging [1-20] vary considerably from species to species and, to a lesser extent, from strain to strain

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within a single species. To avoid distortion of fact, comparisons have been made here only when these and other conditioning factors appeared to be similar. In general, during aging there is a trend towards the replacement of reticular fibrils by collagen and organized connective tissue, often associated with discernible alterations in the blood supply to the part.[3, 5, 6]

A. The Gonad. Specific changes in the genital tract include thinning of the epithelium and of smooth muscle.[7-9] These are the basic atrophic changes; the many variants in the individuals of both sexes are manifold. Therefore a detailed description will not be attempted, as it would serve only to take us far afield at this point.

B. The Pituitary. In the pituitary, there occurs a slowly progressive increase in the reticular fibers surrounding the sinusoidal capillaries, with very little collagenous change [10] and a progressive decrease in eosinophils,[11] if not in all cellular structures,[12, 13] with vacuolation of the basophilic elements.[14]

In the rat and fowl, the early effects of gonadectomy upon the pituitary are a decrease in eosinophils, a hypertrophy and hyperplasia of the basophilic elements and, later, widespread vacuolation of the latter. In the aging rat, Wolfe [11] found a decrease in eosinophils but no increase in basophils, although vacuolation similar to that following gonadectomy did occur. In the fowl, Payne [12] observed with aging a regression in all three types of cells; further, he noted that gonadectomy accelerates the appearance of the alterations which are histologically characteristic of the hypophysis of the senescent animal.

The histologic evidence in the pituitary of aging has been partially reversed by the use of testosterone propionate,[4] particularly as regards an increase in eosinophils towards levels found in younger animals. Estrogen has the same effect [21] "in low concentration," [22] but reduces the number of acidophils if large amounts are employed.[4, 22] In other words, in small doses estrogen tends to stimulate the acidophilic cells and furthers the secretion of luteinizing hormone (LH), while inhibiting the basophilic cells but not depressing the secretion of follicle stimulating hormone (FSH).[22] If the dosages are sufficiently large, all gonadotrophic function, including FSH production, can be suppressed.[2, 22]

From the above, it would appear that the long term effects of castration upon the pituitary in the adult animal are not unlike those to be seen during aging, although appearing more rapidly and varying in degree; furthermore, these are at least partially reversible if *proper* doses of gonadal hormones are used.

C. The Adrenal. In the adrenal, during aging, there are a progressive increase in the width of the capsule, and a gradual conversion of reticulum into collagen, most marked in the reticular and least pronounced in the fascicular zones,[5] inversely varying in the fascicular zone with the degree of vacuolation [3] and mitotic activity.[2, 15, 16]

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The alterations which Dribben and Wolfe [5] connected with "advancing age" in the rat included (1) progressive increase in the width of the capsule; (2) gradual transformation of reticulum into collagen and an increase in the thickness of the collagenous fibers; (3) a slow progressive thickening of the reticular fibers of the glomerular and fascicular zones, "but the degree of coarsening was not pronounced and there was little tendency for the reticulum to be transformed into collagen," and (4) conspicuous coarsening of reticular fibrils and an increase in the density of the reticular network of the zona reticularis, with collagenous fibers appearing relatively early in adult life. Korenschevsky and his associates [2] found that in the female rat some of these changes were partially reversible by the use of testosterone, and were more conspicuously altered when this was employed in combination with estrogen, progesterone and androsterone. These alterations towards normal were most marked in the fascicular and glomerular zones, probably the most actively involved in the adjustments of the climacteric. Furthermore, Korenschevsky, Paris and Benjamin [2] considered the changes in senescence similar to those seen in younger animals deprived of their gonads, and noted that "on the whole, changes in the administration of hormones in the adrenals of senescent rats were similar, but for some hormones (estradiol and thyroid) weaker than those obtained in ovariectomized animals treated with the same hormones or their combinations."

The Thyroid. In the thyroid during aging, one finds a diminished follicular size, a lessened amount of colloid tinctorially pale to the ordinary stains, atrophied glandular epithelium, and a diffuse increase in the interacinar connective tissue.[2, 23]

In the female rat, these changes have been partially reversed by the use of androgen, estrogen or progesterone, with decreasing potency in the order named.[2]

During aging, changes in the thyroid are very closely connected with those in the adrenal, particularly with the activity of its fascicular zone.[24] Overactivity of this portion of the adrenal usually evokes a similar hyperfunction in the thyroid, and vice versa. The obverse is also true; a lowered function of the adrenal cortex may be associated with hypothyroidism, the so-called Schmidt syndrome,[25] while primary hypothyroidism is usually attended by atrophy of the fascicular zone. Under normal conditions, senescence results in a lowered activity of the thyroid, with little change in the appearance of the fascicular zone of the adrenal. If the "slowing" thyroid is capable of response to the well sustained adrenal activity, then hyperthyroidism may result and some of the conditions now looked upon as diseases of adaptation may occur. Certain forms of hypertension and diabetes mellitus may serve as examples. Whether underfunction or hyperfunction of the thyroid and adrenal cortex occurs during the post-climacteric period may depend upon the degree of activity displayed by the pituitary, particularly in relation to its production of adrenotrophin or adrenotrophins.[24]

II. Functional Alterations of Endocrine Glands During Aging

Considerable effort has been made to determine the variations in the functions of the glands of internal secretion during aging, particularly by attention to tissue biopsies, metabolic balances, tests of functional capacity and urinary hormonal excretion rates in normally and abnormally aging individuals. The present report deals with the beginning of studies by the two last mentioned methods in 76 presumptively normally aging persons (41 men and 35 women) between the ages of 44 and 85 years, and in 158 patients (45 men and 113 women) suffering from one of the following conditions: the climacteric, hypertension, arthritis, diabetes mellitus, Achard-Thiers syndrome and senile osteoporosis. Urinary gonadotrophins were performed according to the method of Klinefelter, Albright and Griswold [26];

Table I

Results of Hormonal Assays in Normally Aging Subjects

Women (35)				
Age	Urinary			
	Gonadotrophins (m.u./24 hours)		17-Ketosteroids (mg./24 hours)	
Years post-menopausal	>53	<53	>10	<10
0–3	4	2	5	1
3–5	4	7	8	3
5–10	1	8	5	5
10–20	0	7	1	6
>20	0	2	0	2
45–55	4	9	11	2
Years	Men (41)			
45–55	4	9	11	2
55–65	4	8	7	5
>65	0	16	6	10

total 17-ketosteroids by the short procedure developed in our own laboratories [27, 28, 29]; 11-oxycorticoids in accordance with the determination of Heard and Sobel,[30] with extraction modified for adaptation to our own facility, and salt tolerance as suggested by Soffer and his associates.[31]

Table 1 shows a summary of the results of urinary assays for gonadotrophins and 17-ketosteroids in relation to age at the time of the determinations. In all subjects at all ages the basal metabolic rates were within the usually accepted normal limits; the urinary 11-oxycorticoids were likewise within the normal range in those upon whom they were performed. In this table, the words "menopausal age" are taken to mean the first three years immediately following the cessation of menstruation, and the other ages

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mentioned for women are in each instance in relation to this figure. The average menopausal age for the group was 47.1 years. It will be noted that high titers for gonadotrophins were observed in both men and women, although much more frequently in the latter. Furthermore, with increasing age these values tended to decline, and in later life were usually normal in both sexes. All the figures for the excretion of 17-ketosteroids fell within the normal range, as may be seen by reference to previously reported values.[29]

Laboratory data from those suffering from a disease state common to aging are contained in table 2. In the category "climacteric" we have placed 113 women and 45 men who, on clinical grounds and in relation to their response to therapy, were justifiably considered to be suffering from endocrinologic changes resulting in the characteristic picture of this condition. The urinary excretion of gonadotrophins was determined and found to be normal in three of five women, and in five of six men. In these few instances, the severity of the symptoms bore no direct relationship to the

TABLE II

Several Diseases Common in Declining Years

Disease	No. Subjects	Direction of Alteration in Urinary						B.M.R.			Positive Salt Tolerance
		11-Oxycorticoids			17-Ketosteroids						
		Norm.	Low	High	Norm.	Low	High	Norm.	Low	High	
Climacteric	104	11	1	2	49	35	20	59	16	18	3 of 8
Hypertension	10	3	1	1	10	0	0	7	2	1	8 of 10
Arthritis	15	4	0	0	11	4	0	8	7	0	7 of 9
Diabetes mellitus	17	3	0	3	12	2	3	12	1	2	—
Achard-Thiers (?)	5	1	1	3	1	0	4	1	0	4	2 of 4
Osteoporosis	7	0	0	2	2	4	1	2	2	0	1 of 4

severity of the manifestations. It is of further interest that 20 of the subjects showed a high excretion for 17-ketosteroids, while 10 of these were among those who had an increase in basal metabolic rate.

Of 10 hypertensive patients (seven men and three women) whose condition was reliably believed to have had its onset at 45 years of age or after, eight had a positive salt tolerance test. However, no other significant correlation could be made between the duration or severity of the hypertension and the other data here recorded.

Arthritis, sometimes mixed but usually of an osteoarthritic type, was present in 15 subjects (six men and nine women). There was no correlation in four subjects between the moderately lowered excretion of 17-ketosteroids and the severity of their disease. The disease was mild in the two subjects responding negatively to the salt tolerance test, but was no more severe in three of the remaining seven who were subjected to this procedure. Four of the seven subjects who had low basal metabolic rates also showed an abnormally low excretion of 17-ketosteroids.

A high excretion of 11-oxycorticoids was found in three subjects within the first several days following recovery from diabetic coma. There was no correlation between the diabetic status and the excretion of 17-ketosteroids, although nine of the 12 subjects for whom this figure was recorded as normal exhibited values well below the mean normal levels.

In only two cases was the 11-oxycorticoid excretion determined in osteoporosis; it may be significant that in both of these the figures were high. As reported in the literature, the subjects with low values are believed to have had the most severe forms of the disease.

We have labeled as the Achard-Thiers syndrome five women in whom mild diabetes mellitus, hypertension, minimal hirsutism and varying degrees of obesity appeared at or shortly after the menopause. Strictly speaking, probably only one of these belongs in the group described by Achard and Thiers, as she alone had a tumor of the adrenal, benign in type and apparently functionally active. It appears to us significant that in this disease there was a tendency for an elevated excretion of 11-oxycorticoids and 17-ketosteroids, as well as for a positive salt tolerance test and an increased basal metabolic rate.

III. Discussion

Attempt has been made in figure 1 to exemplify several hormonal relationships as they probably occur in the normal adult female. While most of the experimental data on which this is based has been obtained from work with small laboratory animals, certain fundamental facts appear to be applicable to the human being on the basis of clinical observations.

Pituitary gonadotrophins stimulate the ovary to the production of estrogens and progesterone. The latter appears to exert little effect upon the pituitary [32]; on the other hand, estrogen serves as a regulator for the production and release of the pituitary gonadotrophins. If the amounts of estrogen are very large, all gonadotrophic activity can be suppressed,[22, 32, 33] although luteotrophin (LTH) secretion may be undisturbed.[32] In somewhat lessened doses, FSH production is increased by estrogen. Still lower concentrations stimulate the production of luteinizing hormone (LH).[22, 34]

In addition to the above actions, estrogen appears to be a stimulant to the formation by the pituitary of ACTH [32]; androgen, at least in large doses, suppresses ACTH formation.[35, 36] Thus perhaps is explained the slightly larger size of the adrenal in the female, and its hypertrophy in the male castrate. Normally, however, these actions are counterpoised in such manner that ACTH,[32] somatotrophin (STH) [34] and possibly LH [22, 32, 34, 37] are produced in the proportional quantities necessary to maintain a normally functioning adrenal. During the period of active sex life, estrogen concentration is sufficiently high to nullify some of the LH action upon the adrenal which appears to play a rôle in stimulating those adrenal cells concerned with the production of sex-linked steroids. At the same time, estrogen furthers the predominant action of ACTH upon the production

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and release of 11-oxycorticoids, as well as its lesser but apparently also important synergistic action upon the somatotrophins in the control of mineralocorticoid formation and release.

Direct and indirect interactions by way of the pituitary between the gonad, the adrenals and the thyroid also serve to influence materially the function of the suprarenal gland.[38-some of the lit. cited]

The net result of all the actions and interactions above described is a balanced regulatory influence upon secondary or target organs, tissues and

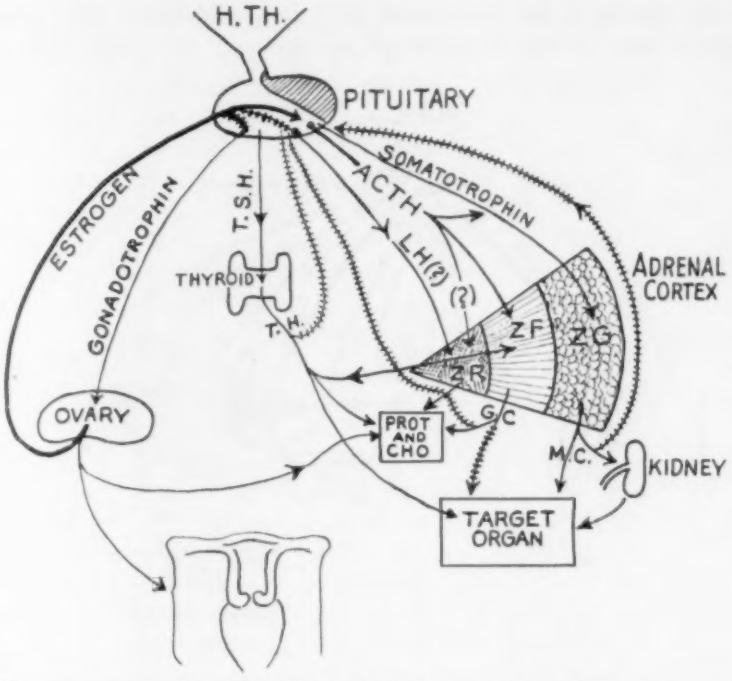

FIG. 1. Schematic representation of the relationships between the pituitary, ovary and adrenal glands prior to the climacteric.

Key: H.Th., hypothalamus; T.S.H., thyrotrophin; T.H., thyroid hormone; L.H., luteinizing hormone; ACTH, adrenicotrophin; Z.R., zona reticularis; Z.F., zona fasciculata; Z.G., zona glomerulosa; G.C., glucocorticoid or 11-oxycorticoid; M.C., mineralocorticoid.

functions. For instance, sex hormones, whether derived from the gonad or the adrenal, appear to be predominantly catabolic. In connective tissues, particularly in response to injury, mineralocorticoids and glucocorticoids are, in some respects, complementary and, in others, opposing; the former have been called the "hormones of defense," the latter the "hormones of healing."[34] The former repair the injury; the latter remove the scaffolding and debris concerned in bringing this about. The former favor the deposition of hyalin; the latter oppose such a change or remove it. A balance between these influences on target organs is necessary for health.

Sex differences in interglandular relationships obviously exist, upon the nature of which considerable light has recently been shed.[32, 37] However, at this juncture emphasis should be placed mainly upon the overall balance that obviously must exist to maintain health. Waning gonadal activity in middle or late middle life or the experimental ablation of the gonad appears to initiate alterations in the activities of the glands of internal secretion which require a shifting of function in order that health may be maintained. Some of these changes have been schematically represented in figure 2.

In the female at the menopause there is a diminution, but probably not a complete loss, of the secretion of estrogens of the ovary. The accom-

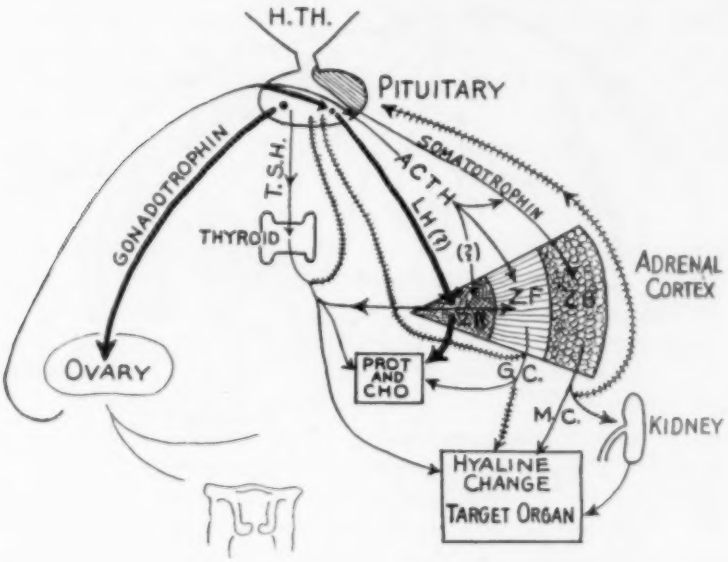

FIG. 2. Schematic representation of the normal adjustments which take place between the pituitary, the ovary and the adrenal at or during the climacteric. See figure 1 for key.

panying high pituitary and urinary content of gonadotrophin, in a major portion FSH, is probably due to underutilization by the ovary,[22, 39] although this is denied by some workers.[32-see discussion] It is interesting to note that in many of the women for whom results were reported the urinary gonadotrophins were not high. We believe this is in part due to the period of time elapsing between the menopause and the determination. However, there are conditions, such as ovarian agenesis, in which the titer remains high for years, although even here instances have been reported in which gonadotrophins were not elevated.[40, 41] Attention may also be called to the not infrequent occurrence of high values for urinary gonadotrophins in the male, which are probably associated with or the result of diminishing activity of

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the germinal epithelium,[42, 43] and which are not lowered by any but the very largest doses of testosterone.[44] With the loss of ovarian function following the menopause, there is evidence to suggest that the estrogen titer remains sufficiently high to stimulate the LH factor of the pituitary [23, 45]; or both FSH and LH may be concerned.[46, 47] In any event, the net result appears to be a stimulation of the activity of the adrenal directed toward the production of estrogen- and androgen-like materials [32, 37] which may act upon a potential X-zone, even in the mature animal,[32] or upon the cells of the reticular zone, which are probably closely akin to the interstitial cells of Leydig in origin and function.[48, 49]

These changes in hormone production have at times been associated with a temporary increase in the excretion of 17-ketosteroids postmenopausally (table 1),[50] but the general trend for urinary 17-ketosteroid values is downward from middle age onward.[29, 51–54]

Thus it is seen by reference to figure 2 that the loss of the anabolic effects of sex hormones is compensated at least in part by the adrenal cortex, a fact which has led Hamblen [55] to speak of the adrenals as the "gonads of the aged." Normally, in aging, the adrenal probably does not produce as much estrogen as the fully functioning ovary, so that the estrogenic stimulation of ACTH production is lessened.[32] Not only is the stimulation of the pituitary probably decreased, but there is also some evidence to suggest that this gland is less responsive, at least as regards the release of ACTH under the influence of epinephrine administration,[56] while the adrenal maintains its ability to react vigorously to ACTH,[56, 57] unless there is some interfering disease present.[58] Thus, the overall activity of the adrenal is decreased in consonance with the diminution in the general activity of the aging individual. Thus, too, a reasonable balance between anabolic and catabolic activity is maintained. Since mineralocorticoid production is less controlled by ACTH than is that of the glucocorticoids, there is a tendency in the aging subject for the occurrence of hyalin changes in target organs. In all of these normally occurring alterations the thyroid undoubtedly has a distinct rôle,[59] in which influences acting mutually amidst gonadal, pituitary and adrenal activity are concerned. Upon these, present studies have shed no light.

In view of the well demonstrated powerful influences of the adrenal steroids, it seems not only possible but probable that maladjustments in the shifting of certain functions from the gonad to the adrenal after the menopause or in the climacteric may play a part in the production of some of the diseases that are not uncommonly associated with aging. In the spectrum of tests available to us (table 2), including a few determinations of urinary gonadotrophins, it is suggested that, during the period of active climacteric symptoms, urinary gonadotrophins are usually high in women and normal in men; 11-oxycorticoid excretion is usually normal in both sexes; 17-ketosteroid output is altered from the normal range of values in more than 50 per

cent of the subjects of both sexes, although higher than normal figures are more common in women; the basal metabolic rate is normal in two-thirds of all subjects, and the response to administered desoxycorticosterone acetate (DCA) and salt is usually normal.

In considering diseases of adaptation, Selye [60] has summarized evidence tending to connect certain cases of cardiovascular disease and arthritis with an overproduction of mineralocorticoids of the adrenal gland. While climacteric and post climacteric arthritis may not correspond to the condition which he has described, it is nevertheless interesting that, of the 15 subjects with a

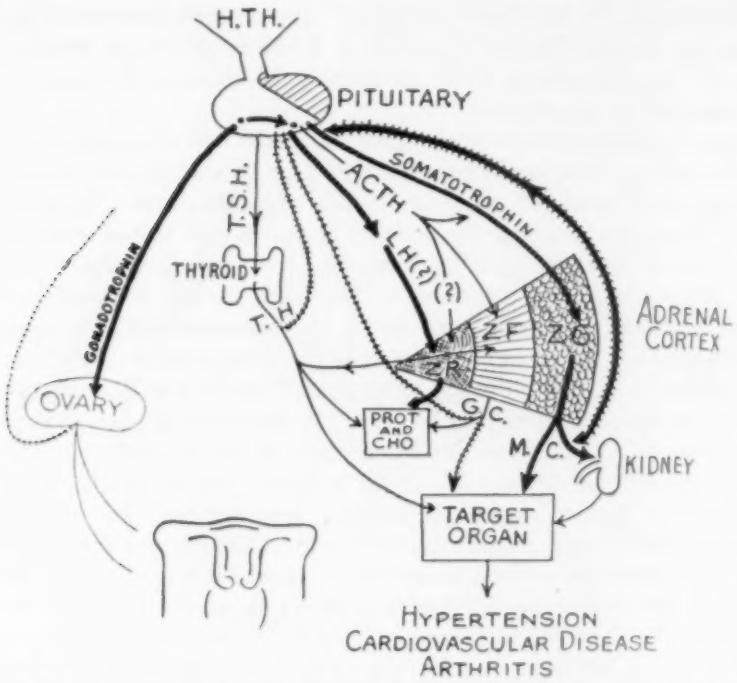

FIG. 3. Schematic representation of some glandular maladjustments in diseases which are common in late middle life with a predominant production of mineralocorticoids by the adrenal cortex. See figure 1 for key.

predominantly hypertrophic form of the disease first appearing in or past the climacteric, no significant changes occurred in 11-oxycorticoid excretion, while one-fourth showed a low level of 17-ketosteroid excretion, one-half a lowered basal metabolic rate, and 77 per cent an abnormal response to the administration of DCA and salt (table 2).

Of 10 subjects with hypertension first recognized following the onset of the climacteric, 80 per cent gave an abnormal response to the ingestion of salt and DCA, but showed no change in the basal metabolic rate or the urinary excretion of 17-ketosteroids or 11-oxycorticoids. These changes

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suggest, though we do not think they prove, an overproduction of mineralocorticoids; the altered hormonal picture is schematically represented in figure 3.

In patients who had suffered from diabetes mellitus, the Achard-Thiers syndrome or osteoporosis, there was some, though perhaps equivocal, hormonal assay evidence of an overproduction of 11-oxycorticoids by the adrenal cortex, a high excretion being present in 61 per cent of the subjects tested. This was associated with an altered output of 17-ketosteroids in 50 per cent of the patients. The probable secretory alterations are schematically represented in figure 4.

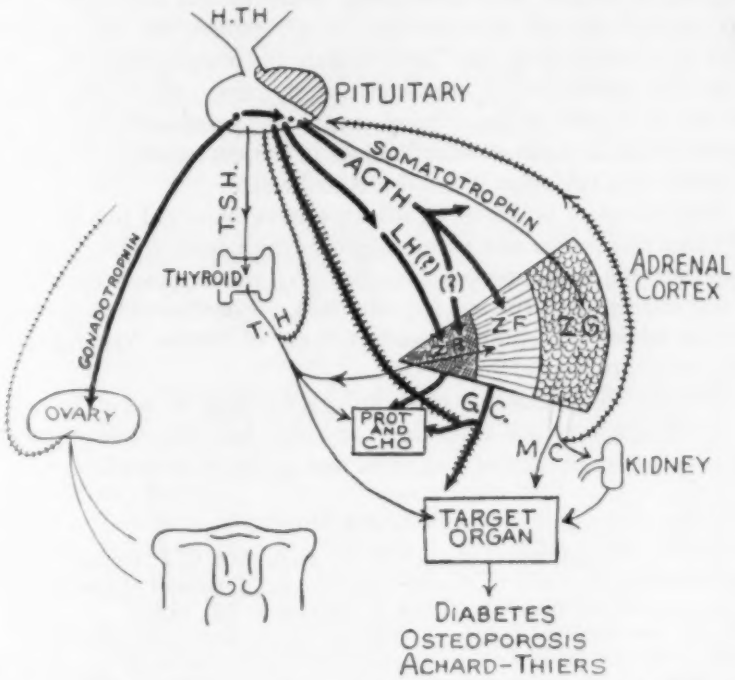

FIG. 4. Schematic representation of some glandular maladjustments in diseases which are common in late middle life with a predominant production of glucocorticoids by the adrenal cortex. See figure 1 for key.

Many types of conditioning factors enter into the processes concerned with aging. This is true even in relation to the glandular changes touched upon in the present discussion. Very little of the available factual data in the endocrine field has been analyzed, but some pertinent correlations have been attempted. The trend of these changes is in its turn influenced widely and profoundly by heredity and environment, using each of these two terms in its broadest possible sense. The present objects have been to indicate the complexity of the problem; the necessity for individualization of therapy

in the illnesses of aging which may be associated with glandular disturbances; the potency of the tools available, and the possible association of the onset of active clinical manifestations of aging with the climacteric syndrome.

SUMMARY

1. Histologic changes in the endocrine glands of aging subjects have been summarized, and attention has been called to the similarity of these changes (in kind but not in degree, at least as regards the female rat) to those which follow ablation of the gonad.

2. In 41 men and 35 women who appeared to be "normally aging," there was a gradual decline with increasing years in the excretion of urinary gonadotrophins and 17-ketosteroids. High values for the former were observed in a majority of the "immediately postmenopausal" women.

3. In 104 subjects with climacteric symptoms, only a small percentage showed any alteration in the urinary output of 11-oxycorticoids; 53 per cent revealed a variation from standard values in the excretion of 17-ketosteroids, and 37 per cent a variation in basal metabolic rate.

4. Alterations of probable significance were observed for (a) the excretion of 11-oxycorticoids and 17-ketosteroids in diabetes mellitus, the Achard-Thiers syndrome and osteoporosis, and (b) the response to administered DCA and salt in arthritis and hypertension. For this study, patients were selected in whom the clinical manifestations of illness occurred during or following the climacteric.

5. The possible endocrine relationships existing in normally and abnormally aging subjects are discussed, and the fact that many conditioning factors play a part in normal and abnormal aging is stressed.

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MEDICAL PROBLEMS IN RADIOLOGICAL DEFENSE*

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Introduction

The need for disaster planning and organization has been exemplified in recent years by such occurrences as the Cocoanut Grove Fire in Boston, the Texas City and Perth Amboy explosions, and other similar holocausts. These taxed medical facilities to the limit, yet the number of casualties involved represents only a small fraction of the number to be expected if a well planned and executed atomic attack were to be successfully launched against one or more large cities of the United States. Saturation bombing of London, the fire-bomb raids on Tokyo and the atomic bombings of Hiroshima and Nagasaki created disasters of great magnitude. Our British friends were well organized and rescued many, but our (then) Japanese enemies were not prepared. Hundreds, if not thousands, of lives were lost in Japan which could have been saved if appropriate action for rescue and casualty treatment had been planned and taken.

In our defense against atomic warfare the medical profession must play a leading rôle in both planning and execution.

When the bomb explodes, there is a sudden release of energy which in a nominal bomb can be compared to the explosion of 20,000 tons of TNT.

When detonated in the air, an incandescent "ball of fire" is produced which within one second has expanded to about 900 feet in diameter and which has attained a luminosity (as observed from 5.5 miles away) of approximately 100 times that of the sun. Temperatures of approximately 300,000° C. are attained. Radiations of ultraviolet, infrared and of ionizing gamma rays are also emitted. Neutrons are scattered which bombard other particles of matter, making them also radioactive. A shock-wave of terrific intensity is produced. The "ball of fire" rises, first at a rate of 200 miles per hour, and then more slowly, creating its own atmospheric chimney as it goes and continuing to emit ionizing radiations dangerous to people below for some 90 seconds. A mushroom-like cloud is formed which contains radioactive fission products and atmospheric particles which have been vaporized. Within 10 to 15 minutes the cloud reaches the stratosphere, where these dangerous particles are diluted and dispersed.

The physical effects which will be observed upon the terrain beneath an air burst can be correlated with the medical effects upon personnel by considering three major physical effects: blast (which produces mechanical trauma), thermal radiations (which produce burns), and ionizing radiations (which produce radiation sickness). The distances at which these energies

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are effective in producing their disaster effects vary with the "power" of the bomb and the altitude at which the bomb is exploded. Marked increases in the power of such bombs would produce relatively moderate increases in the radii of destructive effects. In fact, to increase the effective radius of damage by a rough factor of two, a bomb eight times as powerful as a nominal bomb (such as those used in Japan) would be required. The most effective utilization of the weapon against a heavily populated area is an air detonation at considerable elevation above the target. The results of an explosion of a nominal bomb at about 2,000 feet altitude are now considered.

Blast Effects

A shock wave of great pressure proceeds outward peripherally from the center, with rapid reduction in force as the distance is increased. This shock wave, traveling with the speed of sound, is comparable to a moving wall of compressed air which exerts its effect over a brief but appreciable time interval (about one second), in contrast to the trip-hammer effect of conventional munitions. Most damage is done by the sustained positive pressure, although some destruction may result from the negative or suction phase which follows, and which is of about three seconds' duration. In Japan, at 2,000 feet from the ground zero, reinforced concrete buildings collapsed. At 7,000 feet, brick buildings were badly damaged and frame buildings destroyed beyond repair. At 10,000 feet there was marked blast damage to the majority of frame houses. The blast effect upon human beings may be classified as *direct* or *indirect*.

Direct injury, such as rupture of the stomach or other viscera, trauma to lungs and rupture of eardrums, might be expected as a result of the compression by air blast near ground zero, but except for a few ruptured eardrums there was no evidence of such at Hiroshima or Nagasaki.

Indirect blast effects, on the other hand, caused thousands of traumatic casualties, and occurred as the result of objects being blown against humans or of humans being blown against objects. The blast-equivalent of wind of over 800 miles per hour velocity may occur near the ground zero, which concentrically decreases in intensity to about 200 miles per hour one mile away, and to 70 miles per hour at a distance of two miles. Flying wreckage is hurled which injures and kills. Contusions, lacerations and fractures are the injuries to be expected. Few leg fractures were seen in Japanese hospitals, because rescue was not organized and such casualties died in the resultant fires or from shock or other causes.

Thermal Radiation Effects

Infrared and ultraviolet radiations emanate from the ball of fire. These radiations burn instantly, since they travel with the speed of light, but the effect may extend over a period of a few seconds.

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A high percentage of the significant heat energy which will affect people on the ground is expended during the first second, and the remainder during the next two seconds. Much of the ultraviolet is absorbed by ozone produced by the explosion, but some filters through and may, in combination with infrared, alter the skin pigmentation of exposed individuals.

Depending upon the atmospheric conditions at the time, it is estimated that radiant heat of 3 calories per square centimeter, which will cause blistering burns upon exposed skin, can occur at distances of from one mile on a densely hazy day to two and one-half miles on a very clear day. The maximal transmission occurs on the days in which the visibility is greatest.

The medical effect of severe second-degree flash burns caused by energies of 10 calories/cm.^{2} can occur at 7,000 feet from the ground zero on an average clear day upon the exposed skin which is directly in the unobstructed path of the rays. Uncovered skin on the opposite side of the body (away from the burst) will be normal. Shadow effects are noted; for example, an ear may be burned but not the skin behind it. The brim of a hat can protect the upper part of the face, but the chin and neck may be severely burned. Such burns thus are caused by radiant heat, as distinguished from an envelope of hot gases.

At 4,500 feet from ground zero, the khaki G. I. uniform probably gives adequate protection, since it takes about 14 calories/cm.^{2} to ignite it. Within a half-mile of ground zero, many or most combustible materials will burst into flames unless shielded from the direct rays; thus clothing affords little or no protection.

The general statement may be made that light-colored clothing is more protective than dark-colored clothing. The former reflects the heat radiations and the latter absorbs them and may even ignite. Burns under the darker portions of cloth can result.

Tight-fitting clothing affords less protection than loosely worn garments. Any nontransparent material interposed between a person and the bomb will protect against the burning rays. Clothing may afford protection from the flash but, if clothing ignites, then burns due to actual flame may result. Thus two classifications of thermal injury occur: flash burns and flame burns. The former are caused by direct injury of tissue by radiation from the "ball of fire," the latter as a secondary result of flames of combustible materials ignited by the flash. Even though many of the resultant fires may be snuffed out by the ensuing blast effect, some will persist and may be fanned into even greater fury. Stoves are upset and gas lines disrupted. Secondary fires result in which trapped persons are burned. Rescue must be attempted before the fires spread.

Brief mention may be made here of the effect of the brilliant visible light upon the eyes. The wink reflex may protect against conjunctival burns, but a temporary dazzling or loss of vision may be experienced by those who happen to be looking directly at the flash. This may persist for from several minutes to a few hours, until the body replenishes the visual purple.

Ionizing Radiation Effects

During the explosion of an atomic bomb, certain nuclear radiations are emitted as a result of the fissioning of the uranium or plutonium. In an air burst at 2,000 feet altitude, the clinically important ionizing radiations are the gamma rays. These are essentially similar to x-rays, and occur in adjacent portions of the electromagnetic spectrum, but they are of shorter wave length. The effects are similar except that gamma rays are more energetic and more penetrating, and are capable of effect at greater distance. The "ball of fire," or the fission-product substance within it, continues to emit this type of radiation during its ascent. People on the ground are affected over an interval of one and one-half minutes, after which time the emanating source has risen "out of range." Something on the order of 50 per cent of this radiation, which is received at ground level, is attained within the first second, 80 per cent in 10 seconds, and the remainder in the interval up to 90 seconds. Thus there is a little time after the brilliant flash of an explosion is observed in which to take some cover or some evasive action, such as rolling into a ditch. It must be appreciated, however, that these rays are very penetrating and are capable of passing through quite a few inches of concrete or earth, but many of the rays will be absorbed in passing through such thickness. The more material one can place between himself and the fireball, the greater the success of the evasive action. The example is often cited that gamma radiation would prove fatal to one-half of the people exposed at 3,000 feet from the explosion even if protected by 12 inches of concrete, whereas 30 inches of concrete would adequately protect. Each inch of steel or three inches of concrete or four inches of earth constitute what is referred to as a "half thickness," because they are capable of absorbing roughly 50 per cent of radiation passing through them.

The unit of measurement of gamma rays is the roentgen, just as it is for x-rays. Unshielded individuals within about one-half mile from ground zero of a nominal air burst would receive 700 roentgens or more of whole body radiation, which is considered the LD 100 (lethal dose for all exposed). Death ensues within about two weeks.

Unshielded individuals only a few hundred feet farther away from ground zero would receive around 450 roentgens, which is considered to be the LD 50 dose, or the dose sufficient to kill about 50 per cent of untreated resultant cases. Proper therapy of this group could probably save many lives.

Unshielded individuals at about three-quarters of a mile from the center would receive around 250 roentgens, which is considered to be the median sickness dose (MSD). About one-half of these would become ill with radiation sickness but with a good prognosis, provided secondary infection is prevented or adequately treated.

Symptoms of radiation sickness are:

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1. Nausea and vomiting, occurring two or three hours following exposure and during the first day.
2. Apparent recovery, which results in a symptom-free or latent period, varying in individual cases from about two days to three or more weeks and depending chiefly upon the dosage of ionizing radiation received.
3. General malaise, loss of appetite, fever, severe inflammation of the mucosa of the mouth and throat, marked pallor, diarrhea, nosebleed and petechial hemorrhages.
4. Epilation, which may begin about the eleventh day.

The explanation of these symptoms is readily apparent when it is appreciated that rapidly reproducing cells, such as those of the hematopoietic system, the intestinal mucosa and the hair follicles, are selectively more sensitive to damage by ionizing radiation than are most other cells or tissues of the body.

The therapy of radiation sickness in most cases may be postponed for a few days following the disaster, during which interval greatest attention must be given to therapy of burns and traumatic casualties.

The treatment of radiation sickness consists of general supportive measures, such as bed-rest, nursing care and an adequate diet, including vitamins and readily absorbable foodstuffs, bearing in mind that there may be severe damage to the intestinal mucosa. Adequate fluid intake, parenteral fluids and repeated whole blood transfusions, to maintain a hemoglobin level of about 10 gm., may be life-saving. Antibiotics, especially aureomycin, should be used both to prevent and to treat intercurrent infection.

Beyond one mile from ground zero, the total body gamma radiation dosage is not clinically significant.

It is of interest here to point up the fact that the blast effects producing injuries of clinical significance and thermal radiation causing blistering burns may occur up to two and one-half miles. Thus it is logical to presume that the great majority of casualties to be seen by the physician will be trauma and burns, and that relatively few, perhaps only 15 to 20 per cent, will be due to ionizing radiation. In consideration of the tens of thousands of casualties resulting from a successful atomic strike, the smaller percentage of radiation sickness cases may actually be counted in thousands. Ionizing radiation may also complicate other traumatic and burn casualties, creating increased mortality. Many of those exposed to ionizing radiation may migrate many miles during the latent or symptom-free period to the homes of families or friends. Thus it is imperative that physicians everywhere become familiar with the diagnosis and therapy of this syndrome. The history of the exposure should not be hard to get!

Much has been said elsewhere about the "fall out" of radioactive elements from the cloud of an air burst. It is sufficient to make the straightforward statement here that in all probability there will be no significant hazard from

the attainable concentration in such "fall out" of these radioactive elements following an air burst.

At the expense of sounding an alarmist's note, it must be emphasized that now is the time for the physicians of this country to prepare for disaster due to atomic warfare. It could happen here, in one or more of our heavily populated or industrial or governmental centers.

Medical preparedness requires that physicians have knowledge of the effects of the weapon; it requires the training of millions of people in first aid and medical rescue, and in such a training program the physician must participate; it implies advance surveys for emergency location of temporary hospitals, in schools or churches or other suitable buildings located on the periphery of potential blasted areas; it demands readiness to handle and to treat rapidly tens of thousands of traumatic and burn cases and, later, thousands of cases of radiation sickness.

American physicians can and must meet the challenge imposed by the threat of atomic disaster!

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EVALUATION OF ANTIBIOTIC THERAPY IN HUMAN LEPTOSPIROSIS *

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Prior to the advent of antibiotics, many agents were employed for the therapy of leptospirosis. Walch-Sorgdrager [1] some years ago reviewed the earlier literature which described the use of arsenical and bismuth compounds and of immune serum. In brief, none of these earlier remedies has stood the test of time. Moreover, sulfonamides were devoid of therapeutic value.[1-4] Recently numerous investigators have described the beneficial effects of penicillin in human cases. Bulmer,[5] Patterson [4] and Suchett-Kaye [6] concluded that this antibiotic when used during the early stages of leptospirosis, i.e., before the onset of jaundice, was markedly effective in reducing fever, lessening the severity of symptoms and shortening the course of illness; however, they found it to be of little value when employed after the onset of jaundice. In contrast, other investigators were not at all impressed with the usefulness of penicillin in any stage of this disease.[7, 8] Streptomycin was said to be of value in the treatment of one case of leptospirosis,[9] while inconclusive results were obtained in the few patients who received aureomycin.[7, 10, 11]

This report describes studies on the therapeutic effects of five antibiotics in 67 cases of leptospirosis in Puerto Rico. Diagnosis was confirmed by isolation of leptospirae from blood, urine, or spinal fluid, and by demonstration of the development of specific antibodies, or by both procedures. Two of the critically ill cases received cortisone in addition to aureomycin. Finally, 12 additional patients with leptospirosis received no specific therapy and were studied as controls.

Materials and Methods

Selection of Cases: Patients selected in sequence as they were diagnosed were placed in a given treatment group regardless of their age, sex, or the severity of their illness; moreover, treatment of one group was completed before beginning therapy on another group with a different antibiotic. The

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patients were hospitalized in the San Juan City Hospital, Bayamon District Hospital, San Patricia Veterans Hospital, Rio Piedras Municipal Hospital, and the Medical Service of the Rio Piedras Penitentiary. In the latter institution a prison break occurred and 22 fugitives contracted leptospirosis during exposure for one to four days in cane fields while eluding Insular Civil Authorities.[12] The clinical picture of the 79 cases in the series was variable, and in many the definitive diagnosis, based on laboratory investigations, was not established until after the patients had recovered. However, each treated group, except that given aureomycin and cortisone, included cases with only mild febrile illness without jaundice and others with severe disease.

Laboratory Diagnosis: Either direct culture or animal inoculation [13] was employed for the isolation of leptospirae from blood, urine, or spinal fluid. The development of specific antibodies in the sera of patients was measured

TABLE I

Number of Leptospiral Isolation Attempts on 65 Treated Patients

Material	Procedure	Day after Treatment Began													
		1	2	3	4	5	6	7	8	9	10	14	21	28	35
Blood	Culture	33	29	10	22	9	22	10	9	23	19	30	33	14	5
	Animal inoc.	14	32	10	16	6	19	9	5	18	17	18	22	14	4
Urine	Animal inoc.	10	17	7	17	7	20	5	3	12	12	16	26	14	5
C.S.F.	Culture	2	2	1	3	0	1	0	1	1	0	1	0	0	0
	Animal inoc.	2	2	1	3	0	1	0	1	1	0	1	0	0	0

by the Schüffner-Mochtar microscopic agglutination technic [14] which employs living leptospirae. Direct darkfield examination of the patients' blood, urine, or spinal fluid proved of no value due to artefacts too often confused with leptospirae, an observation previously reported by other investigators.[15, 16]

In this series of 67 treated patients, attempts were made to isolate leptospirae from the blood of 65, from the urine of 55 and the cerebrospinal fluid of 12. Cultures of spinal fluid and blood were made and animals were inoculated with blood, urine, and spinal fluid immediately before therapy was initiated. Cerebrospinal fluid was collected and examined only from those patients who displayed marked signs of central nervous system involvement. Table 1 summarizes the types and number of tests performed on the designated day after therapy was begun; it indicates that repeated examinations were performed over a period of time. The results of the

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tests are correlated with the clinical findings elsewhere in the text and the comparative diagnostic value of the different procedures is discussed in another paper.[13]

In general, similar isolation procedures were employed in the 12 control cases who received only supportive treatment, the tests being carried out on the first, second, fifth and tenth days after hospitalization. Additional urine examinations were performed on two of the patients in this group who were found to excrete leptospirae for variable periods of time.

Technics employed to demonstrate leptospiremia, leptospiruria, or the presence of the organism in the spinal fluid are described in detail elsewhere.[13] In brief, they are:

Cultural Process: One drop of freshly drawn whole blood was inoculated at the bedside into two vaccine bottles, each containing 10 ml. of Fletcher's media.[17] In addition, defibrinated blood was taken from the bedside to the laboratory and one drop (larger quantities are undesirable) inoculated into 10 ml. of both Fletcher's media [17] and Schüffner's media as proposed by Davidson.[18] The same technics were employed when spinal fluid was examined. Direct cultures of urine gave unsatisfactory results due to bacterial contaminants; therefore, this procedure was abandoned. All cultures were incubated at 25° to 30° C. in the dark and were examined by darkfield illumination on the tenth and thirtieth days after inoculation.

Animal Inoculation: Guinea pigs (150 to 200 grams) and hamsters (25 to 35 grams) [19-21] were employed in animal tests for isolation of leptospirae. Defibrinated blood, cerebrospinal fluid, and urine were injected intraperitoneally in the following amounts:

	Guinea Pig	Hamster
Blood	1.5 ml.	1.0 ml.
CSF	2.0 ml.	1.0 ml.
Urine	3.0 ml.	1.0 ml.

The animals were bled on the fourth day after inoculation and one drop of heart's blood was cultured in 10 ml. of Schüffner's and 10 ml. of Fletcher's media, respectively; these cultures were incubated and examined as previously described. At the beginning of this study all experimental animals were sacrificed on the fourteenth day and suspensions of liver and kidney were cultured for leptospirae. This procedure was discontinued when it became evident that the leptospirae could be grown from heart's blood taken on the fourth day from all animals which yielded the organism in cultures of their tissue.

Serologic Tests: Blood for serologic studies was obtained on the same day the initial cultures were made and at regular intervals thereafter. Serial specimens of sera from all patients were examined by the Schüffner-Mochtar technic for specific antibodies against *Leptospira icterohaemorrhagiae, L. canicola* and *L. bataviae.*[22]

Plan of Treatment: The daily dose of antibiotic and the duration of ad-

ministration varied within certain of the treated groups. At the beginning of this study, antibiotics were administered until one day after the patient became afebrile; the course of therapy varied from three to five days. This regimen was considered to be inadequate and a more prolonged schedule (eventually 14 days) of therapy was instituted.

Chloramphenicol: Eighteen patients were treated with chloramphenicol.* Six of this group received the medication for 14 days, eight for a period of seven to 12 days, and four for three to five days. Members of the second subgroup had been assigned the 14-day course of therapy, but seven of them left the hospital prematurely because of apparent clinical recovery, and one succumbed to the infection on the seventh day of treatment. Oral medication was used whenever feasible; however, three patients in this treated group were given the antibiotic intravenously or intramuscularly for several days before oral therapy was instituted. In general, the therapeutic regimens consisted of an initial loading dose of 2.5 to 3.0 gm. (50 to 75 mg. per kilogram of body weight) followed by 1.0 gm. every eight hours. The mean duration of treatment for the group was 9.6 days and the mean total dosage was 26.6 gm.

Aureomycin: Thirteen patients were treated with aureomycin †; seven of this group for 14 days, five others for slightly shorter or longer periods, while one received the antibiotic for only four days. The average duration of treatment for this group was 15 days, with a mean dosage of 36 gm. of aureomycin. Early in the study four patients received 2.0 gm. orally as an initial dose and 2.0 gm. daily, but this dosage was subsequently increased. Eight other patients were given 3.0 gm. as a loading dose and 1.0 gm. every eight hours. The patient who was treated for only four days received a total of 2.0 gm. of aureomycin administered intravenously.

Penicillin: Five patients were treated intramuscularly with procaine penicillin for from five to 20 days with total doses which ranged from 1.5 to 16.9 million units. Mean values for daily and total dosage were 550,000 units and 6.5 million units, respectively, given over an average of 11.8 days.

Terramycin: Terramycin ‡ was administered orally to eight patients; seven, with an initial loading dose of 2.0 to 3.0 gm. and subsequent doses of 1.0 gm. every eight hours. The other was given 3.0 gm. as an initial dose and 1.0 gm. every six hours. The average total dosage was 45 gm. given over a mean of 14 days.

Streptomycin: Twelve patients received streptomycin intramuscularly in amounts of 1.0 gm. every eight hours for three doses, and subsequently at the rate of 1.0 gm. every 12 hours for 14 days. The total dosage per patient was 30 gm.

Combined Aureomycin and Streptomycin: Combined therapy was administered to nine patients; seven for 14 days, one for 13 days and one for

* Supplied by Parke, Davis and Company.
† Supplied by Lederle Laboratories Division of American Cyanamid Company.
‡ Supplied by Charles Pfizer and Company.

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10 days. All patients were given 3.0 gm. of aureomycin and 1.0 gm. of streptomycin per day with the exception of two who received 2.0 gm. of streptomycin daily.

Cortisone and Aureomycin: Two critically ill patients were treated with cortisone * and aureomycin. One died four hours after the initial dose of aureomycin and cortisone, while the other survived, receiving 600 mg. of cortisone in two days and 39 gm. of aureomycin in 14 days.

Criteria for Determining the Severity of Disease: The severity of disease was estimated by both clinical signs and laboratory tests. The temperature, liver size and tenderness, jaundice and manifestations of central nervous system involvement provided clinical data for estimating the severity of the disease; whereas hepatic function tests, urinalysis and blood urea nitrogen were employed as laboratory criteria for this purpose.

TABLE II

Criteria Employed for Estimating Severity of Illness

Designated Values of Severity	Fever (F. °)	Hepatic Involvement						Renal Involvement			CNS Involvement
		Liver-Clinical			Liver-Laboratory			Urine		Blood	
		Size*	Tenderness	Jaundice	Icteric Index Units	Thymol Turbidity Units	Serum Bilirubin Mg. %	Albumin	Cells and Casts	Urea Nitrogen Mg. %	
+ =	99–101	1	+	Subclin.	10–30	3–5	1–5	+	Occ.	15–25	Mild headache
++ =	101–103	2	++	Mild	31–60	6–7	6–10	++	5–10	26–40	Severe headache, dizziness
+++ =	103–105	3	+++	Mod.	61–100	8–10	11–15	+++	11–20	41–60	Confusion, disorientation
++++ =	>105	4	++++	Severe	>100	>10	>15	++++	>20	>60	Coma

* Numbers indicate fingerbreadths below costal margin.

To facilitate interpretation of data, the severity of the illness was recorded as one to four plus for fever, hepatic, renal and central nervous system involvement. The ranges of the various types of observation which are included in arriving at the estimates of severity are given in table 2. An ultimate designation of two plus for liver involvement for a given patient represented an average, arrived at by inspection of the various clinical and laboratory observations listed under the "Hepatic Involvement" column in table 2. Such interpretative estimates were performed for each patient in the present study. The resultant numerical values for each patient in the given therapeutic group were averaged in order to obtain an over-all estimate of the severity of disease in that group. Admittedly, this is a rather cumbersome and inaccurate method but the marked variability of the clinical disease required that an attempt be made to estimate the intensity of the illness.

* Supplied by Merck and Company, Inc.

Results

Effects of Antibiotics on the Course of Disease: The clinical responses of 67 patients to the various therapeutic regimens are summarized in table 3. There was little variability in the effects of the different therapeutic regimens upon the febrile course of the illness and, hence, they have been considered for the moment as one large group. The total duration of fever (day of disease treatment began plus days of fever after treatment) in the groups treated with the various antibiotics varied from 7.3 to 11.4 days with a mean of 9.2. The mean duration of fever in the 12 untreated patients was 8.6, but it should be noted that the members of this group suffered a somewhat milder disease as regards parenchymal involvement than did those in the treated groups. Thus, the duration of fever did not vary appreciably in the treated and untreated cases. The mean total duration of hospitalization was 10.5 days for the untreated group while the treated group on the average remained for 13.7 days after the initiation of therapy. This last value, however, is more of a reflection of the duration of therapy than the severity of disease.

Jaundice was detected clinically in 28 of the 67 treated patients while none of the 12 untreated cases had this sign. The incidence of icterus in this series of 79 patients is approximately 35 per cent which compares with the 40 per cent incidence reported by Schüffner [23] and 50 per cent by Walch-Sorgdrager [1] but is appreciably less than 90 per cent observed by Broom and Alston.[24] The low incidence of jaundice in the present series is undoubtedly a reflection of the careful laboratory studies which made possible absolute diagnosis in the milder form of disease. The clearing of jaundice or improvement in the hepatic function tests showed no uniform relationship to the antibiotics used. The duration of jaundice ranged from 8 to 40 days with an average of 24 days for the 28 patients. Eighteen patients showed an increase in icterus or developed jaundice while on treatment. These cases were distributed rather uniformly throughout the therapeutic groups.

None of the antibiotic agents employed appeared to have any effect, either beneficial or untoward, upon the degree of renal involvement of the patients. The blood urea nitrogen values ranged from 12.3 to 117 mg. per cent in the treated patients. Five members of this general group had uremia and two of these died. Irrespective of therapy, albumin and cellular elements were observed in the urine of 45 of the 67 treated patients from two to 14 days after onset. The 12 untreated patients had blood urea nitrogen ranging from 14 to 20 mg. per cent. These individuals also displayed albuminuria and cellular elements in their urine from three to 14 days after onset of illness.

Headache and definite nuchal rigidity were present in 12 of the 67 treated patients. Five of these had pleocytosis in the spinal fluid of more than 10 cells. The total counts ranged from 10 to 184 per ml. and the cells were almost entirely lymphocytes. Leptospirae were isolated from the cerebrospinal fluid of eight of the patients with nuchal rigidity; one of these

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TABLE III

Therapy of Leptospirosis in Clinical Evaluation in Puerto Rican Cases

Drug	No. of Patients	Severity of Disease				Mean Day of Disease Rx Begun	Duration of Days Rx	Mean Days of Fever After Rx Started	Mean Days in Hospital After Rx Started	Complications
		Fever	Hepatic	Renal	CNS					
Chloramphenicol	18	+++	++	++	+	6.6	9.6	3.0	14.4	1 death 12th D.D.
Aureomycin	13	+++	++	++	+	7.9	15.0	2.0	15.0	0
Penicillin	5	++	++	+	+	4.2	11.8	3.7	13.8	0
Streptomycin	12	+++	+	+	++	8.5	14.0	2.9	14.5	1 phlebitis. 1 cystitis. 1 eye invol.
Terramycin	8	++	++	+	+	6.4	14.0	1.9	14.0	0
Aureomycin and streptomycin	9	++	++	+	+	8.3	13.0	2.0	14.8	0
Aureomycin and cortisone	2	+	++++	++	++++	6.5	7.0	.8	10.0	1 death 7th D.D.
Total treated	67					6.9		2.3	13.7	
Untreated	12	+++	+	+	+	No therapy		Mean days fever 8.6	Mean days in hosp. 10.5	1 carrier (renal 53 days)
Total	79									

D.D. = Day of Disease.

was without pleocytosis. As judged by clinical means, the central nervous system manifestations were not noticeably shortened by antibiotic therapy. Headache and meningismus were present in three of the 12 untreated patients. The persistence of these signs appeared to be directly related to the duration of fever.

The mortality rate for this series was 2.5 per cent which contrasts to 9.4 per cent encountered in the 808 patients reviewed by Walch-Sorgdrager [1] and 6.8 per cent among the 132 cases observed by Gardner and Wylie.[25] The two deaths which occurred under our observation are discussed under the paragraph "Complications."

Effect of Antibiotics on Persistence of Leptospiremia: When it became evident from ordinary clinical observations that no appreciable benefit was derived from therapy, attempts were made to evaluate the usefulness of the

TABLE IV

Results of Therapy on Persistence of Leptospira in Blood, Urine and Spinal Fluid

Drug	No. of Patients With Leptospirae at Beginning of Treatment			Mean Day of Disease Treatment Started	Mean Duration of Treatment in Days	No. of Patients With Lepto. 24 Hrs. or Longer After Treatment Started			Range in Days of Persistence of Lepto. After Treatment			Last Day of Disease Leptospirae Observed (Mean)		
	Blood	Urine	CSF			Blood	Urine	CSF	Blood	Urine	CSF	Blood	Urine	CSF
Chloramphenicol	9	1	1	4.75	11.2	6	0	1	1–3	0	2	6.0	4	6
Aureomycin	7	0	2	5.2	11.2	5	0	2	1–3	0	1–4	6.2	0	8
Penicillin	3	0	0	3.3	13.7	2	0	0	2–12	0	N.D.	7.6	0	0
Streptomycin	1	0	N.D.	5.0	14.0	1	0	N.D.	1	0	N.D.	6.0	0	0
Terramycin	4	0	2	5.2	14.0	2	0	N.D.	2	0	N.D.	6.0	0	4.5
Aureomycin and streptomycin	4	0	1	5.7	13.0	0	0	N.D.	0	0	N.D.	5.7	0	5
Cortisone and aureomycin	1	0	2	6.5	7.0	0	0	0	0	0	0	6.0	0	7
									After Onset					
Untreated	7	2	—	No Treatment		—	—	—	2–7	11–53	N.D.	4.0	32	0

N.D. = Not Done.

drugs through their effect on the continued presence of leptospirae in the blood, urine, or spinal fluid. A tabulation of data from these studies is summarized in table 4.

Twenty-nine of the 67 treated cases had leptospiremia when therapy was begun, between the first and eighth day of disease. In 16 of these positive cases, leptospiremia was still present for at least 24 hours after treatment was instituted. Usually leptospirae disappeared from the blood stream within several days but in one treated patient it persisted for 12 days. Irrespective of the type of therapy or the time at which it was begun, the average value for the last day of disease on which leptospirae were demonstrated in the blood was approximately six days with a range of 5.7 to 7.6.

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This compares with an average duration of four days in the seven positive cases of the clinically milder untreated group.

Leptospiruria was an infrequent finding. Only one of 67 patients in the treated groups had leptospiruria prior to therapy and none after therapy. This contrasts with two of 12 cases with leptospiruria in the untreated group, one for 11 days and the other for at least 53 days.

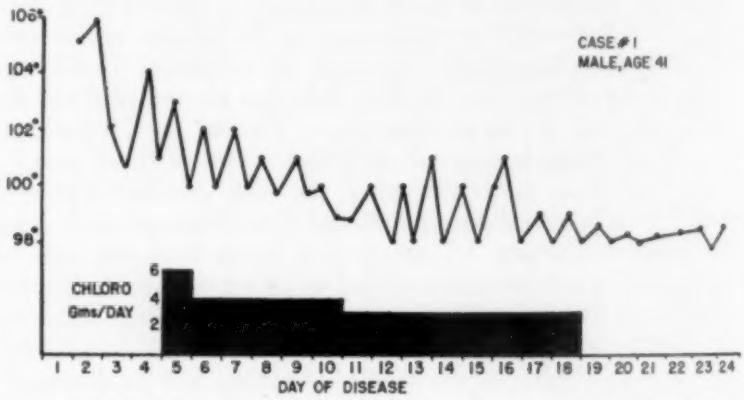
Persistence of leptospira in the cerebrospinal fluid followed the same pattern as found in the blood. Leptospirae were isolated from the cerebrospinal fluid of eight patients at the beginning of therapy and persisted in three of these for from one to four days.

Serologic Studies: Seventy-seven of the 79 cases showed significant rises in leptospiral antibody titers during the course of observation. Forty-two of these developed antibodies against *L. icterohaemorrhagiae* and seven against *L. bataviae.* Twenty-seven patients displayed significant titers of antibodies for two strains of leptospira. There were 17 who had agglutinins for both *L. icterohaemorrhagiae* and *L. canicola,* seven for both *L. icterohaemorrhagiae* and *L. bataviae,* one for *L. bataviae* and *L. canicola,* and two for *L. canicola* and an as yet unidentified strain of leptospira. Case 557 (see case reports) illustrates the rise in antibody titers against two strains of leptospira. One additional patient developed agglutinins to a titer of 1:800 against his homologous organism (not yet classified) but his sera did not agglutinate available standard strains of leptospira. Two of the 79 patients did not develop demonstrable leptospiral antibodies. One of these, case 7, was not examined for these antibodies after the fifth day but leptospirae were cultivated from his blood on the fifth and sixth days and were demonstrated in the kidney at autopsy. A specimen of blood from the final member of the group during convalescence yielded an as yet unidentified leptospira; the patient did not acquire antibodies against this organism. The significance of the presence of dual antibodies in the sera of certain patients and the identification of the as yet unclassified organism will be discussed in other publications.[26, 27]

Complications: Several of the 79 patients suffered from complications and two died. A 52 year old male critically ill with jaundice, anuria and coma succumbed on the seventh day of disease four hours after the initial dose of aureomycin and cortisone. Permission for autopsy was not granted. The second patient, a 46 year old chronic alcoholic male, with severe hepatic and renal involvement, succumbed to the infection on the twelfth day of disease after seven days of chloramphenicol therapy. The clinical description of this patient, case 7, is presented in the section on illustrative case reports and his findings are summarized graphically in figure 2. One patient suffered from each of the following complications: Phlebitis, cystitis, and iridocyclitis. The first two responded to conservative measures but the patient with dimness of vision eventually developed clouding in the anterior chamber of the right eye which persisted during several months of observations.

Illustrative Case Reports

Case 1. The patient, a 41 year old male, was admitted to the hospital on the second day of disease with an illness characterized by sudden onset of chills, fever, headache and prostration. The temperature was 105.5° F., pulse 120 and respirations 25. The pertinent positive physical findings were dehydration, lethargy, conjunctivitis and erythema of the neck, face, shoulders and upper chest. The findings persisted and on the fourth day epigastric pains and diarrhea prevailed and the liver was felt two fingerbreadths below the costal margin. Leptospirae were isolated from the cerebrospinal fluid and blood taken on the fifth day after onset, at which time 3.0 gm. of chloramphenicol were administered as a loading dose followed by 1.0 gm. every six hours for five days and then 1.0 gm. every eight hours for eight days. During the next 48 hours, the patient became critically ill with oliguria, intense jaundice, confusion and lethargy, and responded only slightly to stimuli. He showed little improvement during the third day of treatment at which time leptospiremia was again demonstrated. The following day the patient's urine output increased (3,450 c.c.) and there was some return of mental alertness. He continued a febrile course and on the fifteenth day of disease a roentgenogram of the chest showed a pneumonic process in the right costophrenic angle. Convalescence proceeded uneventfully from this point.



CNS INVOL.	+	++				+++	++		+	0	0												
JAUNDICE	0				++++			++++									+++						++
ICTERIC INDEX					50			68									36						28
THYMOL			9.2								6									6.5			
WBC (THOUS.)	12.7			10.9				7.8					8.1				9.4						
Hgb		9.5						13.5					14				14						
UREA N.					55								28										
URINE CELLS & ALB.				+			+	+									+						0
LEPTO ISOL. BLOOD				+			+						0				0						0
LEPTO ISOL. CSF				+																			
	(L. ICTERO)																						
LEPTO. AGGL. ICT.			0				1:50				1:3200						1:6400						

Fig. 1. A patient severely ill with leptospirosis who received 14 days of chloramphenicol therapy without any apparent alteration in the clinical and bacteriological course of the disease.

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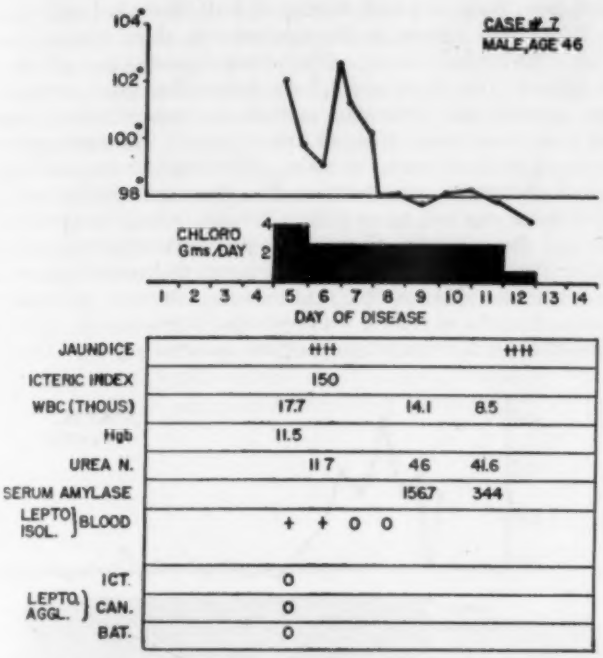

FIG. 2. A patient critically ill with leptospirosis who received 7.3 days of chloramphenicol. Death occurred on the twelfth day of disease.

Case 7. The patient, a 46 year old male, was admitted to the hospital during the fifth day of a disease characterized by weakness, chills, fever, myalgia of the legs, bloody diarrhea and jaundice. The patient admitted to an alcoholic consumption of two and one-half pints of rum per day. The temperature was 102° F., pulse 130, blood pressure 110/70 mm. Hg. and respirations 28. The positive physical findings were dehydration, bulbar and palpebral conjunctivitis with intense greenish-orange jaundice of the sclera, skin and mucous membranes, abdominal tenderness and a tender liver palpable two fingerbreadths below the costal margin. No enteric pathogens were demonstrated in bacteriological cultures of feces. Leptospirae were isolated from blood taken on the fifth day after onset and 3.0 gm. of chloramphenicol were administered as an initial dose and 1.0 gm. every eight hours. There was no change in the clinical condition except that the temperature returned to normal on the eighth day of illness. On the twelfth day of disease the patient developed extreme abdominal distention which was thought to be caused by acute gastric dilatation. The left diaphragm was elevated and the chest was clear to auscultation and percussion. The pulse was irregular and showers of extrasystoles were noted. The patient vomited copious amounts of coffee-ground material, soon followed by vasomotor collapse and death. The infecting strain of leptospira was discarded before taxonomic identification was established. No samples of the patient's serum taken after the fifth day of illness were available for subsequent serologic studies.

Autopsy: (Performed by Dr. E. Koppisch, Professor of Pathology, University of Puerto Rico School of Medicine.) *

* We are grateful to Dr. Koppisch for permission to reproduce an abstract of his report which is in the files of the Department of Pathology, University of Puerto Rico School of Medicine, and the San Juan City Hospital.

Gross description: Body of a well developed, well nourished male with generalized rigor mortis. There was icterus of the conjunctiva, skin, mucous membranes and subcutaneous fat. Abdominal cavity: The stomach and some of the loops of the intestines were dilated. The liver was 1.5 cm. below the costal margin. Heart: The epicardium was smooth and glistening and in the subepicardial tissue along the coronary sulcus were many small areas of hemorrhage. The myocardium was hypertrophic, and greenish-reddish-brown in color. The microscopic findings of the heart revealed a layer of edematous tissue between the serosa and the epicardium which was infiltrated with lymphocytes and monocytes. The interstitial tissue of the myocardium was edematous and the muscular fibers contained perinuclear brownish lipochrome granules. Aorta: The aorta had a moderate amount of hemorrhage in the adventitia of the thoracic portion. Microscopic examination showed a markedly thickened intima, and narrowed media in places, with hydropic degeneration. The vasa-vasorum had dense perivascular infiltration of lymphocytes and monocytes. The lungs appeared

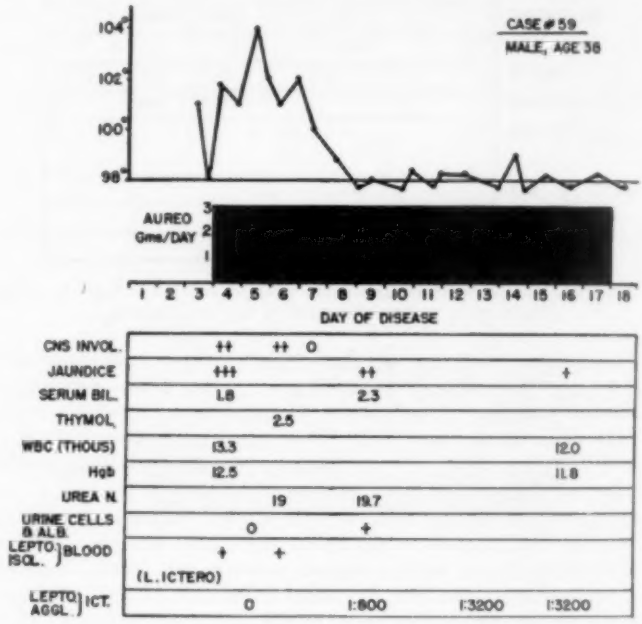

FIG. 3. A patient with leptospirosis who received 14 days of aureomycin therapy with no apparent effect on the duration of leptospiremia or the clinical course of the disease.

normal on gross inspection but the microscopic examination showed moderate congestion. Congestion and fibrotic changes were seen in the spleen. The pancreas was soft and pale greenish in color with small areas of hemorrhage throughout. Microscopic examination showed an increase in the interstitial tissue which was edematous and hemorrhagic. The liver weighed 1,670 grams, the capsule was smooth and glistening, while the cut surface was a greenish-reddish-tan with exaggeration of the lobules. Microscopic examination showed congested sinusoids, cloudy swelling of the hepatic cells and dissociation of the hepatic cords in the middle and central zones. Kidneys: The left and right kidney weighed 220 grams and 125 grams, respectively. The capsules stripped with ease; the surface was yellowish-green with bright red pin-point mottling; and the cortical markings were blurred. Microscopic examination

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showed that the collecting tubules were prominent with swollen epithelial lining cells that almost obliterated the lumen in many areas. Many of the convoluted tubules showed desquamation of the epithelial cells, some were filled with free and degenerated cells, other tubules contained cellular and granular casts and coagulated protein, a little of which was also found in some of the spaces of Bowman's capsules. Leptospirae were found lying between the cells of tubules in sections impregnated with silver by the Krajian method. The interstitial tissue was edematous, with small areas of hemorrhage, and infiltrations of lymphocytes, plasma cells and monocytes. Gastrointestinal tract: The stomach, duodenum and jejunum contained a small amount of coffee-ground material and bright red clots, and the mucosa was congested and hemorrhagic. Microscopic examination of the mucosa from the stomach showed autolysis and diffuse infiltration with many round cells. The submucosal layers were markedly congested and edematous.

Final Note: "This is a case of Weil's disease that was typical in both clinical and pathological findings with death on the twelfth day of illness. The renal changes were severe and leptospirae were demonstrated in these organs."

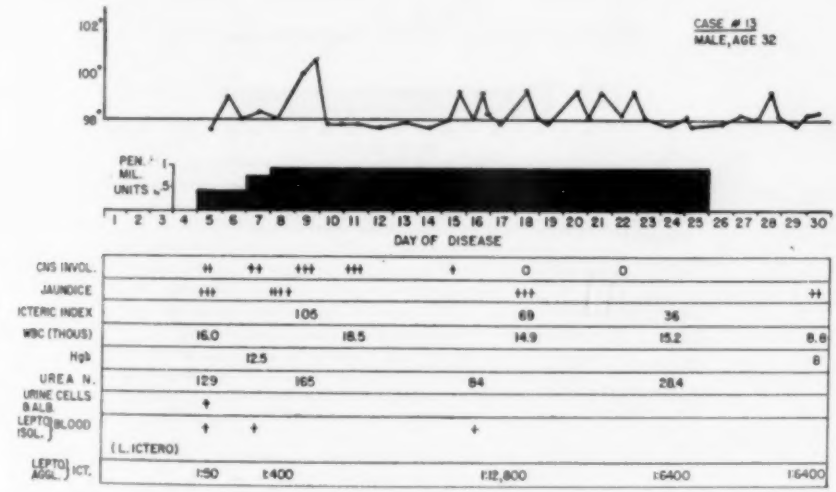

FIG. 4. A patient severely ill with leptospirosis who received 20 days of penicillin therapy, without any effect on the clinical course or duration of leptospiremia.

Case 59. The patient, a 38 year old male, was admitted to the hospital during the third day of an illness characterized by severe headache, myalgia of the neck, back and calves, chills, fever, epigastric discomfort, dark urine and jaundice. The patient stated that his home was infested with rats. The temperature was 101.8° F., pulse 90, respirations 20. The positive physical findings were conjunctivitis, moderate icterus of the sclera, râles in both lung bases posteriorly, upper right quadrant tenderness and a tender palpable liver two fingerbreadths below the costal margin. Leptospirae were isolated from the blood taken four days after onset at which time 2.0 gm. of aureomycin were given as a loading dose followed by 1.0 gm. every eight hours for 14 days. The signs and symptoms persisted through the sixth day and leptospirae were again isolated from the blood taken at this time. The headache and myalgia subsided on the seventh day of disease at which time the temperature began to abate. The patient was asymptomatic during the remainder of his hospitalization except for a mild degree of jaundice.

Case 13. The patient, a 32 year old male, was admitted to the hospital on the fifth day of illness with general malaise, anorexia, diarrhea with 12 to 15 liquid brown bowel movements per day, nonproductive cough, nausea, vomiting, epigastric pain and jaundice. The patient, a plumber, had been working in stagnant water one week prior to the onset of symptoms. The temperature was 99° F., blood pressure 108/74 mm. Hg, respirations 24 and pulse 100. The patient was markedly dehydrated and acutely ill with severe bulbar and palpebral conjunctivitis, deep icterus of the sclera and mucous membranes and a purpuric and petechial rash scattered over the trunk and upper extremities. The heart sounds were regular and rapid, and the abdomen was slightly distended, tympanitic and tender in the upper right quadrant. The liver was extremely tender and enlarged two fingerbreadths below the costal margin.

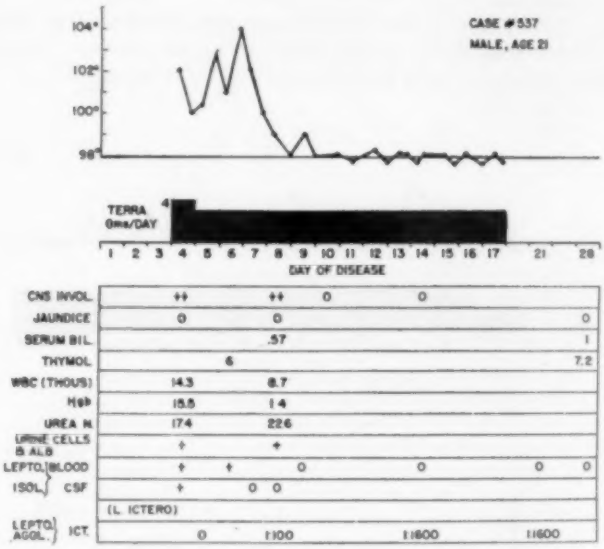

FIG. 5. A patient with leptospirosis who received 14 days of terramycin therapy without any apparent benefit.

Leptospirae were isolated from blood taken on the fifth day of disease. Bacteriological examination of the feces revealed none of the common enteric pathogens. Four hundred thousand units of penicillin were given daily from the fourth to the sixth day. During the sixth day of illness there was deepening of the jaundice, increase in the frequency of vomiting, and the rash became more profuse. The following day he was lethargic and had developed auricular fibrillation, which was confirmed by electrocardiographic tracings. The arrhythmia was controlled with quinidine. Leptospirae were again isolated from blood obtained on the seventh day. During this time the patient had a rather hectic clinical course with increase of icterus, urinary retention and mental confusion. Penicillin was increased to 700,000 units per day for two days and then raised to 900,000 units daily for the succeeding 16 days. On the ninth day of disease the patient became afebrile but six days later he developed a low grade fever which persisted 10 days. Leptospirae were isolated from blood taken on the sixteenth day of illness after the patient had received 9.4 million units of penicillin during 12 days. He was discharged on the thirty-fifth day.

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Case 537. The patient, a 21 year old white male, was admitted to the hospital on the fourth day of disease with the chief complaint of fever, chills, severe pains in the muscles of the back and legs, weakness, anorexia, nausea, vomiting, burning of the eyes, severe headache and reddish colored urine. He was a well developed, markedly dehydrated, acutely ill male with a temperature of 102° F., pulse 100, respirations 20 and blood pressure 110/80 mm. Hg. The other pertinent physical findings were conjunctivitis, nuchal rigidity, epigastric tenderness, and a tender liver two fingerbreadths below the costal margin. Leptospirae were isolated from the blood and spinal fluid obtained on the fourth day of disease, at which time 3.0 gm. of terramycin were given as a loading dose followed by 1.0 gm. every eight hours for 14 days. There was no appreciable change in the patient's condition during the next four days. Leptospirae were again isolated from blood taken on the third day of treatment (sixth day of disease). The headache and nuchal rigidity persisted through the eighth day of illness and disappeared when the fever subsided. The patient was asymptomatic thereafter and further attempts to isolate leptospirae from the blood, urine and cerebrospinal fluid were unsuccessful. He remained in the hospital for completion of the course of the treatment.

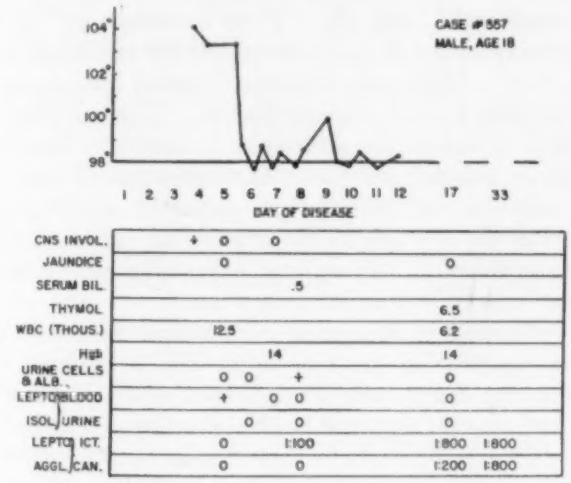
CASE # 557
MALE, AGE 18
104°
102°
100°
98°
1 2 3 4 5 6 7 8 9 10 11 12 17 33
DAY OF DISEASE
CNS INVOL. + 0 0
JAUNDICE 0 0
SERUM BIL. .5
THYMOL 6.5
WBC (THOUS.) 12.5 6.2
Hgb 14 14
URINE CELLS & ALB. 0 0 + 0
LEPTO BLOOD + 0 0 0
ISOL. URINE 0 0 0
LEPTO ICT. 0 1:100 1:800 1:800
AGGL. CAN. 0 0 1:200 1:800

FIG. 6. A patient with mild, febrile, non-icteric form of leptospirosis who received no specific treatment. Note the precipitous fall in temperature and the disappearance of the leptospiremia.

Case 557. The patient, an 18 year old male, was admitted to the hospital on the fourth day of a disease characterized by general malaise, anorexia, headache, chills, fever, myalgia of the back and calf muscles, aching of the eyes and epigastric pain. The temperature was 104° F., pulse 100 and respirations 28. Physical examination revealed dehydration, tarsal and bulbar conjunctivitis and a tender liver which was palpable one to two fingerbreadths below the costal margin. Leptospirae were isolated from blood taken on the fifth day of disease. The patient received no antibiotic therapy. Nevertheless, there was amelioration of the symptoms with a rapid drop of temperature on the fifth day of illness. Additional attempts to isolate the organism were unsuccessful. The patient was discharged from the hospital on the twenty-first day of disease. This patient developed antibodies for both *L. icterohaemorrhagiae* and *L. canicola*. The infecting strain was discarded without detailed antigenic study and classification.

Discussion

Penicillin, streptomycin and aureomycin have been demonstrated to have a beneficial effect on animals infected experimentally with leptospirosis. Heilman [28] and Alston and Broom [29] observed dramatic therapeutic effects of penicillin in guinea pigs infected with *L. icterohaemorrhagiae*. The results of experimental infections in mice with *L. icterohaemorrhagiae*,[30] in hamsters with *L. canicola* [30] and in guinea pigs with *L. icterohaemorrhagiae* [31, 32] indicate that penicillin probably exhibits a suppressive action on the leptospira if administered before the appearance of jaundice in these animals. The spirochetostatic effect of penicillin in vitro was observed by Alston and Broom [29] and Lu Chang.[32] The beneficial effect of streptomycin in hamsters challenged with lethal doses of *L. icterohaemorrhagiae* was shown by Heilman,[33] and Brunner and Meyer [34] found that streptomycin was effective in clearing the urinary carrier state of hamsters and dogs infected with *L. icterohaemorrhagiae* and *L. canicola*. These investigators [35] obtained similar results with aureomycin and also demonstrated the spirochetostatic action of aureomycin in vitro. Moreover, Heilman [36] found aureomycin effective in hamsters infected with *L. icterohaemorrhagiae*. There is general agreement that the protective action of the antibiotics is markedly decreased after the onset of icterus in infected animals. Chloramphenicol had no protective action against hamsters and guinea pigs inoculated with virulent *L. icterohaemorrhagiae*, nor did it eradicate the urinary carrier state of dogs infected with the same organism.[37] No reports have appeared on the use of terramycin in experimental leptospiral infections.

The results obtained in this study reveal that the antibiotics employed demonstrated no appreciable effect upon the clinical course of leptospirosis in man even when the drugs were administered relatively early in the course of disease. There was no apparent beneficial influence on the febrile course, on prevention or shortening of the period of jaundice, on reduction of central nervous system symptoms, or on lessening of the degree of renal involvement. The duration of leptospiremia and persistence of the organism in the cerebrospinal fluid were not appreciably altered by any of the antibiotics employed. Leptospiruria was not demonstrated in any of the treated cases after initiation of therapy, whereas two of the untreated patients excreted leptospira for a variable period of time. These limited observations on this feature are insufficient to draw conclusions on the efficacy of the drugs in shortening the course of leptospiruria.

Conclusions

Studies on leptospirosis of man in Puerto Rico re-emphasize the variability in severity of this infection and clearly show the difficulties encountered in attempting to evaluate chemotherapeutic agents in this disease. Despite these disadvantages, the observations warrant the conclusion that none of the antibiotics employed in this study is particularly effective in this disease.

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In fact, it is doubtful whether any of the antibiotics employed are worthy of future use in the treatment of patients with leptospirosis. Obviously, a further search for a satisfactory therapeutic agent against leptospirae is indicated. In the meantime, efforts should be devoted to finding methods for supporting severely ill patients during the period of toxic damage to parenchymatous organs and the interval required for repair of these lesions.

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PSYCHOSOMATIC MEDICINE LOOKS AT MEDICAL SPECIALIZATION *

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"PSYCHOSOMATIC medicine no longer needs an apology. It has passed that stage. One may consider the acceptance of this fact as the first phase of the problem. The second phase which we are now entering consists of the task of teaching this new discipline to students and to those physicians who are interested in reorienting themselves to medicine." The above quotation comes not from one of our psychiatric journals but from an excellent and comprehensive article in the American Journal of Medicine.[1]

This paper will concern itself with the problems of this second phase, i.e., the teaching of this new discipline to those interested in reorienting themselves to medicine. It will attempt to outline some of the aspects of this phase and to indicate certain avenues leading to possible resolutions of the problem.

How long has it taken us to pass through this first stage of development and acceptance of psychosomatic medicine? This is a matter of considerable conjecture. Some feel that psychosomatic medicine is a relatively new arrival, perhaps of approximately the same age as that other recent arrival on the medical scene—dynamic psychiatry. To this group, psychiatry, as the study of the morbid personality, has proved the gateway for the introduction of the synthetic point of view into medicine. More properly this might be phrased, "Psychiatry has proved the gateway for the *re-introduction* of the synthetic point of view into medicine."

The over-popularization of certain psychologic discoveries at the end of the Nineteenth Century had created a reaction against psychology and psychiatry by the medical profession. By way of the same reaction, medicine had tended to become more somatologic. The re-appearance of the term "psychosomatic medicine," and of the concept of the psychobiologic unity of the human being, marked a renewed attempt to produce a synthesis of the total reactions of human personality.

To others, however, psychosomatic medicine (like the poor) has always been with us. To this group, Socrates' chiding of the Athenian physicians over 2,500 years ago, with the observation that they couldn't treat the body without treating the mind, was an early statement of the psychosomatic concept. Through the centuries of excruciatingly slow travel along the

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road of medical progress, other beacon lights of the holistic concept have illuminated the way.

The holistic concept, while always present, was emphasized only sporadically, however, through the centuries. As the Nineteenth Century developed, medicine became better oriented to the flourishing sciences of physics and chemistry. Gradually it became a natural science, based on the application of these principles to the living organism.

With the development of the laboratory approach, observation and study of parts of the body and part-functioning came more and more into the foreground, with observation and study of the whole person receding simultaneously into the background and ultimately becoming almost entirely lost to view. The brilliant concepts of cellular pathology advanced by Virchow, and the discoveries of Pasteur and Koch, almost irresistibly forced a further concentration on the part to the neglect of the whole.

With this tremendous accumulation of data about part and part-functioning, the inability of one man to encompass the total body of medical knowledge became more obvious. Here, then, was the impelling reason for the development of our era of specialization, and for the appearance of that harassed paragon, the specialist, whose life is devoted to learning more and more about less and less.

As these fragmenters of the whole person took the center of the stage, their forerunner, the general practitioner, who knew a great deal about the whole person (including his environment) and relatively less about his separate parts, retreated toward the wings. Some of these points of view are well expressed in a recent editorial in the *Journal of the American Medical Association*,[2] from which the following quotation is taken:

"Functional and psychosomatic factors have now been repeatedly demonstrated in most of the disease or pre-disease conditions affecting man, including diabetes, hypertension, ulcers of the stomach and lesser ills. Physicians recognize they are not being faced with incipient conditions to control but with end results to patch. The establishment of a single diagnosis, which is often assumed to be the proper effort, followed if possible by prescription of a specific remedy, fails to meet the total problem of the patient. This method may frequently cure the lesion but not the person.

"Here is a reversal of emphasis away from specialization and toward re-birth of training and prestige of the general practitioner. General physicians of the future may be visualized as practitioners whose training included a thorough grounding in the psychodynamics of personality and general physiology and who are aware of the effects of social, industrial, and political impact of environment generally on health.

"Increased availability of time for study of each patient will be essential to success. In contrast to present trends, this visualizes the general physician as the central figure of a coördinated service; in such a situation, specialists will function in solving special objective, pathologic problems."

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From what has been indicated so far, then, it is apparent that we have now reached a stage in the practice of our medical art and science where separation is gradually giving way to unification. And just as the word "unification" for our Armed Forces has attached to it certain strong emotional overtones, so must it provoke among us, as specialists, many disquieting feelings, and by this token reveal the uneasy peace existing among the brothers in the medical family.

The part of the paper which follows will indicate by clinical illustrations a number of ways in which two groups of specialists have been working in this area to bring about this unification. It will attempt to indicate how they have approached a resolut[illegible] the second phase of the psychosomatic problem, that is, the task of t[illegible]g (themselves) this reorientation to medicine. The two groups of spec[illegible]lists referred to are internists and psychiatrists, and the arena in which this effort is made is the Medical Service of Winter Veterans Administration Hospital.

The following two cases illustrate the more or less traditional approach to clinical problems used by each group and the fallacies in the total care of the patient revealed by this handling.

Case Reports

Case 1. A 29 year old farmer entered the hospital giving a history of attacks of nausea, vomiting and watery diarrhea while with the Army in the Aleutians early in 1943. He had participated in the invasion of Attu; toward the end of the invasion his platoon was ambushed and wiped out, and he was left for dead by the enemy, although actually not seriously injured.

Shortly after this the patient became increasingly "nervous," developed nausea and vomiting, and had to be evacuated. Under psychiatric treatment in Alaska, the nausea, vomiting and nervousness improved but a persistent dia[illegible]rhea developed. After further treatment in the United States, he was discharged with the diagnoses of constitutional psychopathic state, emotional instability and functional diarrhea.

During the next three and one-half years he suffered almost constantly with diarrhea, weight loss, marked nervousness and insomnia, which obviously were the most impressive part of his symptomatology. The diagnosis of nonspecific ulcerative colitis was made repeatedly, and the patient was treated with various measures.

This nonspecific treatment probably was related in part to the overwhelming importance given to his psychiatric complaints by every practitioner who saw him. He entered our hospital with a feeling of hopelessness, appearing chronically ill and somewhat wasted. The physical examination showed slight hepatic enlargement. Sigmoidoscopic examination disclosed an inflamed mucous membrane and numerous ulcers of various size, covered with mucopurulent and hemorrhagic exudate and containing many vegetative and cystic forms of *Endamoeba histolytica*.

A full course of emetine was administered, and the patient made a complete recovery and regained a good part of his weight. Two and one-half years following therapy he is still in excellent condition and holding a difficult job.

This case, in brief, indicates the traditional tendency of the psychiatric specialist to observe the patient through his own "psychiatric microscope." What he sees then is what would be expected on viewing any specimen

through a microscope—a tremendously enlarged, exquisitely detailed view of a very small area, but nothing outside the visual field directly under observation.

After about five years of wasted time and effort somebody (this time the internist) decided to view some other parts of the "specimen." It was only then that the specific etiology of the patient's disease was found and specific countermeasures brought to bear and a "cure" produced.

Case 2. A 29 year old veteran was admitted to this hospital with complaints of cramps, abdominal distention and vomiting which had occurred intermittently for the past five or six years, and more persistently and acutely for the past year following a subtotal gastrectomy.

On admission he was in acute distress because of his abdominal distention and a cramping periumbilical pain. Positive findings on physical examination included two extensive postoperative abdominal scars, hyperactive bowel sounds and roentgen-ray evidence of distended loops of small intestine containing fluid levels.

The patient was seen in surgical consultation and various diagnostic impressions were recorded, among them: (1) postoperative adhesions with partial to nearly complete obstruction, with a recommendation of early operative intervention; (2) gastric-jejunal ulcer following incomplete resection.

Following intestinal intubation with the Miller-Abbott tube as a preoperative measure, the abdomen became flat, and mineral oil injected through the tube appeared in the return from rectal enemata. Subsequent roentgen-ray examinations showed no gastrointestinal pathology, and the patient was transferred to Medicine.

The history elicited here indicated that his present illness had begun early in 1944, when his son died from a head injury following a severe beating from his wife. He was enraged at his wife and wanted to kill her. At this time he suddenly enlisted in the Army "to get away from his wife so he wouldn't kill her."

After his son's death, the patient began to have severe abdominal cramps and vomiting. In November, 1945, while in the Army, he had an appendectomy after an episode of severe lower abdominal pain and vomiting, and a normal appendix was found. The patient said he had been ruminating a good deal at that time about his son's death.

Postoperatively there was much abdominal distention, and the patient had to be returned to the operating room on the first postoperative day for the repair of a dehiscence. It was following this operation that he first noticed *attacks* of abdominal distention.

Finally, in November of 1948, the patient had a subtotal gastrectomy after a number of severe attacks of pain and distention and roentgen-ray demonstration of a duodenal ulcer. The duodenum was opened and no ulcer or scarring was found.

Seven days postoperatively he suffered an evisceration after having been tremendously distended. After a protracted convalescence, the patient was discharged from the hospital. His symptoms continued unabated and he was rehospitalized in May, 1949.

Four months after discharge, he was admitted to this hospital. During his psychiatric study and treatment here, the patient at first insisted that there must be something wrong inside and that he needed an operation. Later, however, he was able to see the relationship between his symptoms and emotional problems, particularly his marital situation.

While under observation on the Medical Service, the patient had two more attacks of abdominal distention.

He was again intubated with the Miller-Abbott tube. Relief from the distention

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was suddenly and dramatically obtained upon the insertion of a rectal tube. On the second occasion, the distention was transient and disappeared spontaneously.

It was learned in a talk with the patient that each of these two attacks had followed immediately upon a telephone conversation with his wife, during which he had quarreled with her about her failure to visit him in Topeka.

The patient himself made a connection between these attacks and the telephone calls to his wife. He further indicated that most of his previous attacks had been similarly related to becoming upset about the way his wife was treating him, and to his being unable to voice his anger against her. The patient said that he never expressed his anger, saying, "The Good Book says you may have angry thoughts, but you mustn't say angry words."

Further discussion revealed that he was extremely inhibited and ashamed about rectal functioning. He constantly inhibited the passage of flatus, feeling that this was one of the most impolite things one could do. While in the Army he had extreme difficulty in finding privacy for moving his bowels. In discussing the previous episode of post-operative wound dehiscence, the patient told of his embarrassment about moving his bowels on a bedpan in the open ward in the presence of other patients and the nurse. The same was true of flatus. It seems undeniable that this inhibition of evacuation of the intestinal contents led to the wound dehiscence in each case.

After further discussion of these factors, the patient said that he felt much better and that his symptoms of periumbilical pain between attacks of distention were also much better. He felt his difficulties could be solved in terms of working through his relationship with his wife, and he asked for discharge from the hospital.

This case, in contrast to the one previously presented, indicates the other side of the coin. Here the medical and surgical specialists "missed the boat" because of their constricted approach to this patient. Because of this, approximately six years of needless suffering were endured by this patient, in addition to two needless operations, each followed by disfiguring and incapacitating complications. It was only when, at long last, the emotional factors were considered and treated that the solution to this puzzling problem was found (this time by the psychiatrist), and the patient was helped to return to a productive place in society.

These two cases, then, illustrate in some measure that neither specialist —the psychiatrist nor the internist—is able to handle certain cases when he tries to evaluate or understand them from the point of view of his own constricted visual field. When he does commit this error, needless suffering, trauma and expense are incurred and the relief for which the patient first sought the doctor is unconscionably denied him.

When, on the other hand, our exhaustively trained and sincere specialist turns his hand to therapy, some equally surprising and uncomfortable consequences of his special attitudes towards patients and their problems come to light. At this point some further case material is illustrative.

Case 3. A 28 year old white male, admitted to the hospital because of a skin rash on his right ankle of about seven years' duration, was found to be an extremely tense, hyperactive, defensive, hostile individual who spoke of his great irritability as a symptom only secondary to his dermatitis.

Physical, neurologic and routine laboratory examinations were within normal limits except for a scaly, excoriated neurodermatitis of the right ankle.

The onset was in 1942, when the patient was ordered overseas to an isolated air base. While on the way to this outpost he developed an itching rash of both ankles, which has been present intermittently ever since. After 27 months overseas on this island, where the morale was extremely low and the aggressive tensions between officers and men very high, the patient was hospitalized for neuropsychiatric study following a brief period in the stockade for assaulting a new recruit.

After being returned to the States, he was given a CDD in 1945, and, since his discharge from the service, has been hospitalized repeatedly. Early this year a saphenous vein ligation was performed for his dermatitis and phlebitis.

At college, in the few months before his admission here, he became increasingly irritable, avoided contact with other students, and was so distracted by the intense itching of his recurrent dermatitis that he was unable to continue with his studies. He was referred for hospitalization by a dermatologist, with a diagnosis of neurodermatitis and recommendation for psychiatric treatment.

The patient was assigned to a psychiatrist and in the early interviews began to verbalize a great deal of hostility. He threatened that if he remained in the hospital he might become assaultive. He was at first resistant to psychological testing, but when he finally accepted it seemed to form a good relationship with the psychologist, complaining to the latter that the psychotherapist did not "tell him anything."

During these months of hospitalization, the lesion improved and worsened without any clear relationship to treatment. At one time the patient indicated a fear that he might lose his pension if the lesion healed. In reaction to this discussion he again became hostile and demanding, and asked for discharge. He later withdrew his request, asking for a different doctor and uttering threats at various times that he might "beat up or shoot the therapist."

He then prevailed on the ward internist to see him. In the first of these hours the patient verbalized his tremendous hostility toward his previous therapist. The internist generally took a rather authoritative attitude toward the patient and his failure to follow treatment recommendations. It was quite striking to observe how the patient seemed to respond to this attitude of the internist, in contrast to his response to the more passive and permissive attitude of the psychiatrist.

When the patient was ordered by the internist to stay in bed, to coöperate with the ward personnel and to follow certain treatment for his lesions, he seemed to lose much of his overt hostility and anxiety. At first the patient continued to request another psychiatrist, but finally he decided he wished to continue therapy with the internist.

During the first two weeks of psychotherapy with the internist, and under a strict régime of medical treatment, the patient's lesion improved remarkably and he seemed much less tense. At the end of about a month he was discharged, improved. The general impression of the psychiatrist was that this patient received more benefit from the internist's authoritarian firmness than from his own previous passive permissiveness, and that the patient's treatment was furthered by the psychiatric insight of the internist and his willingness to take over the psychotherapy.

In this case we see illustrated the fact that, on occasion, traditional, conventional, even technically correct therapeutic efforts sometimes come to naught when one's horizon is limited. The psychiatrist, rushing for his psychologic instruments in his understandable zeal to help, neglected to survey carefully the entire situation of his patient. Had he done so, he would have observed with his psychiatric eye what the internist saw so

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clearly with his intuitive eye: that what the patient really wanted and needed was not a deep penetration into his emotional substrate. Rather he pleaded, symbolically, for a firm but kindly person who would give him a reorientation to the world by showing him that his murderous aggression would not kill people and could be stood up against, and that, therefore, he need not fear it but could work toward redirecting it into constructive rather than destructive and self-destructive paths.

The following clinical material illustrates another aspect of therapeutic failure because of short-sightedness (this time on the part of the internist), followed by dramatic relief when the real problem was treated (this time by the psychiatrist).

Case 4. A 54 year old white married male, who had been admitted to the hospital because of complaints of joint pain and tired feelings in his legs of some years' duration, had been on a medical régime for a month and was about to be discharged, relatively unimproved.

On the day prior to his discharge, the patient was seen by the psychiatrist on the latter's invitation because of an overheard conversation between the patient and his ward internist. A very brief scanning of the history made it seem that there was something remaining unanswered in this man's problem.

The man, married and childless, had worked most of his adult life in a store selling household furnishings and supplies. He was critical of the lack of system and of the personnel working under him, and of their great dependency on him to find lost articles and to keep the stock in good order.

While mentioning this, he told also of the difficulty he had with the owner who, though not working in the store, exercised final authority but changed his opinion from moment to moment. This and other factors created more work for the patient.

At this point the examiner interrupted to speak of men in their middle fifties, of the sexual slowing down, the physical slowing down, and the relative insecurity felt as one reached a less productive age. In addition, this particular man in his middle fifties worked for an inconsistent boss who, by his very inconsistency, threatened the job on which the financial security of the patient rested. When this point was reached the patient wept for a few moments and then, in a much quieter and more serious manner, spoke of his fears that his boss would some day "burn the place down" and that he would then be out of a job.

He felt it would then be much more difficult for him to get a satisfactory job and that he would probably have to take an inferior position and be an "underling" for the rest of his life, with even less security. The therapist became more interpretive at this point, indicating that the patient was doing much running up and down stairs —down to the basement, up to the attic, down to the warehouse, back to the store— in an effort to keep things running smoothly so that the store would be productive and his job secure. The patient added that many nights he couldn't sleep, and that each morning on waking he had to take a hot bath to "liven his legs up enough to carry him through the day."

The patient expressed gratitude for the opportunity to talk about some of his problems, which were truly associated with his age but were disquieting. He felt that it was now up to him to talk with the owner to determine just how much responsibility he had for running the store.

This patient, in follow-up, has continued to work and has now been symptom-free for about six months.

Up to this point, the illustrative material has been designed to show the pitfalls which present themselves to both psychiatrists and internists when they behave as isolated specialists. The disappointing results of their activities are evident in efforts directed to diagnosis as well as to therapy. It might be stated here, in passing, that what is pointed out in reference to the specialties of psychiatry and internal medicine applies, in equal measure, to any other specialty.

In the next paragraphs a case will be presented which, in the handling by both the psychiatrist and the internist, represents a possible approach to the ideal therapeutic effort. In the management of this case, some specific problems will be highlighted and attempts at solution indicated.

Case 5. A 41 year old white unmarried male for some years had had complaints referable to the lumbar spine, generally thought to be Marie-Strümpel's disease. About eight or nine months prior to admission he complained of blurring of vision, followed in about four months by numbness in the left foot, progressing to the right, and followed two months later by severe frontal headache. After careful work-up and study, the doctor told the patient that he had severe hypertension. This upset him very much, and with feeling he recalled the death of his father about 10 years before from hypertension. He sought hospitalization here after being told that he would have to have either "sympathectomy or psychotherapy."

Among the essential physical findings noted were a persistent hypertension, in the area of 200 mm. Hg systolic and 120 mm. diastolic; moderate cardiac enlargement, an electrocardiographic pattern of advanced hypertensive heart disease with left ventricular hypertrophy, hypertensive retinopathy with old hemorrhages and early optic atrophy, and failure to concentrate on Fishberg's test, with specific gravity fixed at 1.010. The diagnostic impression was hypertensive cardiovascular disease, malignant type.

The patient was evaluated psychiatrically as a markedly dependent person with hypochondriacal features and a tremendous preoccupation with his illness. On admission, he became by mutual consent the concern of both the psychiatrist and the internist. The rule of thumb adopted was that in this clear-cut case the internist would handle the problems related to the physiologic alterations within the patient, the psychiatrist those related to the psychologic.

To this end the internist, after his first contact with the patient, left the following standing orders: (1) Regular salt-free diet on the ward. (2) Chloral hydrate at bedtime and repeat in one-half hour if necessary. (3) Elixir of phenobarbital four times a day. (4) Blood pressure four times a day. (5) Laxative. (6) Electrocardiogram in the morning. (7) Cardiac fluoroscopy. (8) Do not tell the patient his blood pressure readings—refer him to me. (9) Attitude toward patient should be one of kind reassurance; let him do the talking. (10) Eye consultation. (11) *Speed the work-up.*

On studying the chart in the morning, the psychiatrist noted these comprehensive orders and felt a rush of emotion compounded of anger, frustration, puzzlement and despair. His first impulse was to rush off to correct what he considered this frontal assault on the patient, but he suddenly sat back and decided to reflect. As a result of these reflections, he waited until his ruffled feathers had settled and then called his medical colleague for an informal conference.

Here he carefully and in accurate language acquainted his colleague with his observations of the patient. He stated that psychologically the patient was a tremendously dependent, passive individual whose wants, for intrapsychic reasons, were

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essentially insatiable. He added that the patient's hypochondriacal symptomatology would reflect any and every aspect of what the patient felt the doctor was trying to find out. He pointed out that the patient's extraordinarily deep and specific preoccupation with his hypertension made the most extreme caution necessary in initiating and pursuing examinations or laboratory studies which could be misinterpreted by the patient.

The results of this conference were a revelation to both the psychiatrist and internist. It became quite clear to both that, while each had apparently entered into the "team" treatment of the patient, they had in fact merely applied again their restricted, specialized point of view. Only after a number of these informal conferences did it become clear to both doctors that, if the patient was to benefit from this combined effort, each had to think not only of his own specialized activities but of what they meant in terms of his team-mate's efforts. Put another way, each had to rise above his preoccupation with those aspects of the patient falling within his field of special competence and to survey carefully and critically *every* aspect of the patient with his illness.

When asked for a critique of this effort, the internist said, "It was necessary for each to consult and learn from the other during the course of treatment.

"Moreover, the patient was suggestible, hypochondriacal and demanding. Anxiety was easily aroused if the physical approach was handled without considering this man's conflicts between passivity and independence.

"I found this an outstanding example of how closely the internist and psychiatrist must of necessity work together. Although they were not necessarily in complete agreement on all points, each could learn from the other and so make possible a unified approach to the patient."

The patient has now been in therapy with this medical-psychiatric team for approximately three months. There has been an inconstant reduction in blood pressure, one reading as low as 140/90. However, there has been undoubted symptomatic improvement, with disappearance of headaches, marked alleviation of joint complaints and the appearance of a definite sense of well being. In brief, the total patient feels better, acts better and is better in relation to himself and the world in which he lives.

In concluding this perhaps somewhat over-elaborated presentation, reference is again made to the opening paragraphs. What has been demonstrated is that, in the application of the psychosomatic point of view, specialists are now called upon to step off their specialistic pedestals and again come face to face with the patient as a whole man.

If they are able to do this successfully, they will learn that they can work closely and coöperatively with their medical colleagues of all persuasions in a "team" effort to bring to their patients that total health implied by the ancients in their motto of "a healthy mind in a healthy body."

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THE EFFECT OF PROLONGED ADMINISTRATION OF THYROID *

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Introduction

The beneficial effects of continued thyroid therapy in patients suffering from myxedema are remarkable and persistent. On administration of relatively small doses, the basal metabolic rate rises and remains within normal limits as long as the therapy is continued. The symptoms and signs of myxedema disappear and do not recur; sometimes a slightly higher dosage of thyroid is required with the passage of time, but the effectiveness of the drug does not change materially. (See figure 1.) On the other hand, as was pointed out in a former report,[1] it is often difficult by the administration of similar amounts of thyroid to maintain an increased basal metabolic rate in those patients that are free of the manifestations of hypothyroidism, whether the basal metabolic rate be initially normal or substandard.

Beginning in 1936, this problem was studied by observing the effects of the continued administration of thyroid to euthyroid patients, the dose being increased in small increments at intervals of many months.[1] On daily ingestion of from 0.5 to 1 gr. of thyroid, most of the patients showed an early rise in the basal metabolic rate, followed by a decline to the initial level in four to six months' time. The continued administration of larger doses of thyroid, which would prove toxic in the early treatment of myxedematous patients, commonly failed also to have a sustained effect. (See table 1, Mrs. R.) After months of treatment the basal metabolic rate had often fallen toward the initial level (figure 2). Furthermore, when thyroid was discontinued after prolonged daily administration of 2 gr. or more, the basal metabolic rate fell to points definitely below the initial values and, in some instances, mild symptoms of hypothyroidism appeared; but this depression was temporary. It was felt that the function of the thyroid gland had been inhibited during the period of prolonged ingestion of thyroid.

This idea was corroborated by Cope, Rawson and McArthur [2] in 1947: a patient with thyrotoxicosis factitia was operated upon as a case of Graves' disease; the thyroid gland was small, and a biopsy was reported as showing "involution." Furthermore, in investigation of patients with a true hyper-

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functioning single adenoma of the thyroid gland, they found that the uninvolved thyroid tissue was atrophied and physiologically inactive in the uptake of a tracer dose of radioiodine; the histologic section showed involution.

In 1945, Riggs, Man and Winkler [3] reported that a concomitant rise in the basal metabolic rate and the serum protein-precipitable iodine occurred when gradually increasing amounts of thyroid, up to 25 gr. daily, were administered to euthyroid patients over a relatively short period. This effect was found to be variable and unpredictable. Noting the ability of euthyroid patients to tolerate huge amounts of thyroid, far exceeding the dosage required for the relief of myxedema, they suggested that the normal gland was able to inactivate administered thyroid hormone.

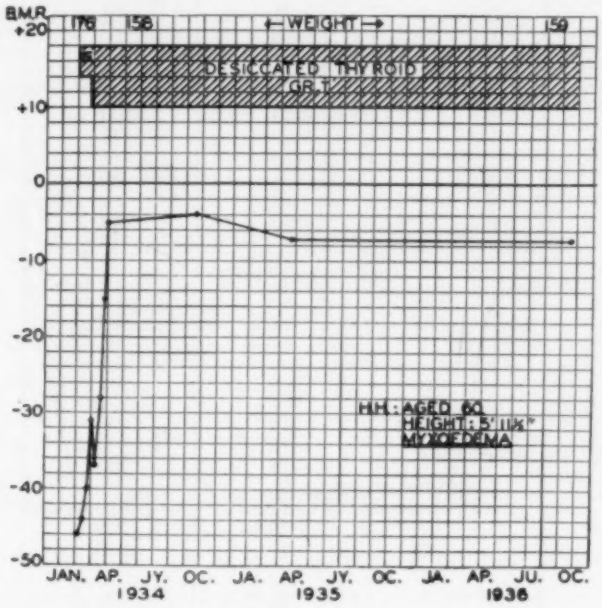

FIG. 1. A myxedema patient maintained for several years on a small dose of thyroid. He later died of myeloid leukemia.

These observations are in keeping with data reported from experimental work. In 1917, Herring [4] showed that, on administration of large amounts of thyroid substance to rats, the thyroid gland appeared to enter a resting phase characterized by a shrinkage of the gland, accumulation of colloid and decrease in the height of the epithelium. In 1920, Loeb [5] pointed out that the feeding of thyroid tablets to guinea pigs had a marked inhibitory effect on the compensatory hypertrophy of remnants of thyroid tissue left after partial thyroidectomy. He later pointed out [6] that, following ingestion of thyroid substance, the presence of thyroid hormone, or of a substance as-

TABLE I

Response to Continued Ingestion of Thyroid in Case of Obesity on Reducing Diet
Case A. R., aged 64 years. Height 5 feet 7 inches. Diet, 1,000 calories.

Date	Desiccated Thyroid	B.M.R.	Weight	Pulse Rate
	Gr. daily	%	*Pounds*	
1938				
Nov. 3			362	70–80
5		−11		
11		−17	354½	60–80
16		−17		
18			351	
26		−5	350½	60–80
Dec. 3		−6		
10		−9		60–80
17		−11	341	
29		−14	341	
1939				
Jan. 7		−21	331	60–80
12		−20		
13	ii			
20		−15		60–80
28		−10		
Feb. 4		−13	323	60–80
10		−19	317½	
18		−13	311	60–80
27		−4	310	60–80
Mar. 7		−12		
17		−13	299	60–80
23	iii			
24		−15		
31		−12.5		
Apr. 6		−9		
13	iv	−12	285	60–80
20		−7	282	
28		−6	280	70–80
May 5		−5	275	
12		−7	272½	
19	Discontinued	−3		
23		−15		
26		−18	265	
30		−18		
June 5		−20.5		
6		−20.5	265	
13		−19	260	60–80
21		−22		
27		−27		
July 4		−24		
12		−25		60–70
15–17			259½	50–70
18–25			258	45–70
Aug. 11		−17		60–80
12	v			
23		−2	255	70–80
31		−4		70–85
Sept. 14		−3		60–85
21		−3	235½	60–76

sociated with it, exerts a continuous depressing effect on the activity of the thyroid gland and, in addition, renders it less responsive to various kinds of stimulation. Smith, Greenwood and Foster [7] (1927) postulated that the tolerance of normal animals to excessive amounts of injected thyroid was

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gained partly by compensatory atrophy of the thyroid gland and partly by some "buffering mechanism." They showed that slightly larger than physiologic doses of thyroid caused a greater rise in the basal metabolic rates of thyroidectomized rats than in the normal, and that large doses had relatively less effect on normal animals than smaller doses. Whatever the "buffering mechanism" might be, it appeared to be less effective in thyroidectomized animals. In the same year, Kunde [8] found that the degree of toxicity produced in the normal dog and rabbit by the ingestion of very large

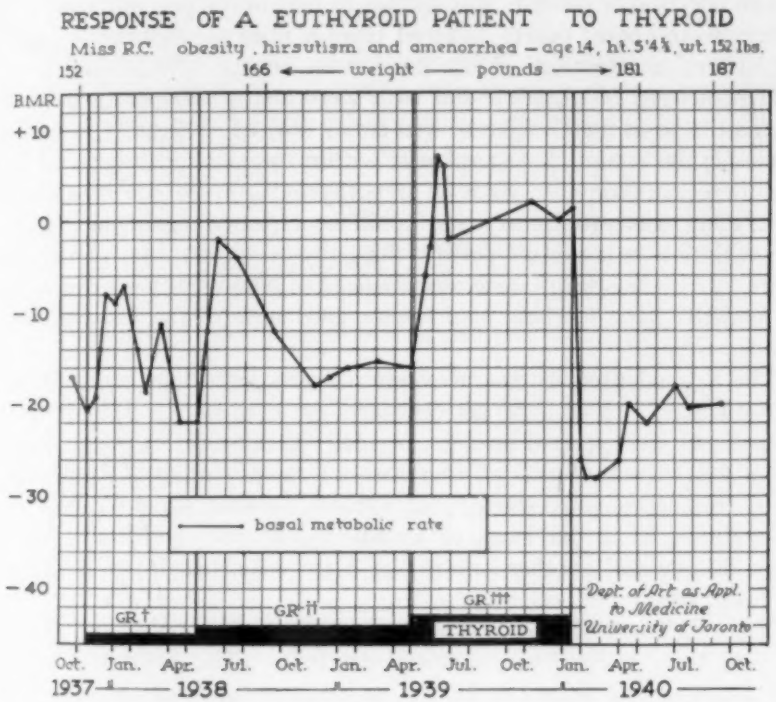

FIG. 2. This patient gained weight on prolonged administration of increasing amounts of thyroid. After discontinuing the thyroid, she restricted her diet, lost weight and began to menstruate again.

amounts of thyroid substance varied markedly in different animals of the same species; it was also noted that the thyroidectomized animals were much more susceptible to large doses than animals with intact glands, and it was suggested that their tissues were more sensitive to thyroid hormone than the tissues of normal animals.

From a review of the literature in 1940, Selye [9] emphasized that endocrine glands in general may be set at rest and even caused to undergo atrophy by administration of large amounts of their specific hormones.

The purpose of this report is to present the results of a continuation of the study of the effects of prolonged administration of thyroid, the dosage

being increased at intervals of several months by larger increments than formerly. An attempt has been made to find how much thyroid can be tolerated by different people. Observations have been made on the clinical condition of the patients, the basal metabolic rate, the serum protein-precipitable iodine, and the thyroid function as determined by the 24 hour thyroid uptake of radioiodine.

Selection of Cases and Methods

The selection of patients was similar to that in the pre-war work. Many of them were obese; others suffered from a mild psychoneurosis and were glad to receive attention. Only those were chosen who wished to remain under prolonged observation and who were able to coöperate well. In all patients the basal metabolic rate was either normal or slightly to moderately decreased; the serum cholesterol was within the normal range, and in none were there symptoms or signs of hypothyroidism. If the basal metabolic rate tracing was satisfactory and could be repeated again and again with little variation in a control period, the daily administration of thyroid was begun. No other drugs were administered. The diets were not restricted. The patients lived in their own homes and came to the hospital regularly for observation.

The thyroid used in this investigation was Canadian Standard thyroid (Parke Davis), which is 50 per cent stronger than the U. S. P. preparation. The patients were started on 2 gr. per day; at intervals of many months the dosage was increased in 2 gr. increments to a maximum of 10 gr. per day. About 16 patients were started; for various reasons, some patients dropped out of the series at one stage or another; only two carried through to the 10 gr. dosage and another one to the 8 gr. dose, but many reached the 4 and fewer the 6 gr. level.

The clinical condition of the patients, including pulse and respiratory rate and body weight, was followed carefully. The basal metabolic rates were taken by one of us (A. H. S.) at frequent intervals, using a Benedict-Roth apparatus. Serum cholesterol values were determined by a modification of the method of Schoenheimer and Sperry [10] in the laboratories of the Department of Pathological Chemistry under the supervision of Professor J. A. Dauphinee. The protein-precipitable iodine of the serum was determined by the method of Salter and Johnston.[11]

Beginning at the time of cessation of therapy, the 24 hour radioactive iodine uptake of the thyroid gland was measured, usually at weekly intervals. The radioactive iodine (I_{131}) was obtained from the Atomic Energy Project, National Research Council of Canada, at Chalk River, Ontario. No carrier iodide was added. A small test dose of 10 to 20 microcuries, diluted with a small quantity of distilled water, was injected intravenously, and the uptake of radioiodine by the thyroid was measured at 24 hours by a lead-shielded Geiger-Müller counter tube at a distance of 6 inches from the center point of

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the isthmus of the thyroid, and expressed as a percentage of the total dose administered. This small test dose of radioiodine has proved to be as efficient in the assessment of thyroid function as larger amounts,[12] and can be repeated safely at frequent intervals.

The radioiodine uptake of a number of other patients who have been receiving constant doses of thyroid, often for several years, was also measured and, beginning in October, 1950, the uptake has been measured in a number of patients in the control periods and in the early weeks of thyroid therapy.

Results

On daily ingestion of 2 gr. of thyroid, most of the patients showed an early rise in the metabolic rate, followed by a gradual decline in four to six months' time to or toward the normal level; no patients presented toxic symptoms. When the dose was increased to 4 gr. per day, the basal meta-

Table II

Miss Z.: Rise in basal metabolic rate and protein-precipitable iodine in steplike fashion with increase in thyroid dosage; no development of tolerance; no decline in basal metabolic rate and protein-precipitable iodine on continued administration at any particular dosage level; symptoms of overdosage with 4 gr. and 6 gr.

Date	Thyroid	Basal Metabolic Rate	Protein-precipitable Iodine	Weight
	Gr. daily	%	*μg.%*	*Pounds*
1948				
Nov. 1	0	−11	4.8	153
Nov. 15		−15	4.9	
Nov. 29		−14	4.7	
Dec. 6		−16	4.6	
Dec. 13		−15	4.7	
Dec. 27		−14	4.7	
1949				
Jan. 10	ii	−16	4.6	
Jan. 17		−14	5.9	
Jan. 31		−15	6.0	164
Feb. 21		+4	5.9	
Mar. 1		0	6.2	
Mar. 15		−2	6.0	
Apr. 4		0	5.8	
Apr. 11		0	5.8	
May 2		0	6.2	
May 23		0	6.1	
May 31	iv			
June 6		+16	8.2	
June 13		+17	8.0	152
June 20		+19	8.4	
July 14			8.4	
1950				
Jan. 12	vi			
Jan. 20			9.8	
Feb. 3		+20	10.3	
Feb. 17		+20	10.3	
Mar. 1		+26	10.2	131

bolic rate and protein-precipitable iodine rose again, usually to higher levels, and, in a few instances, there were toxic symptoms; on continued therapy at this level, both factors gradually fell, with one exception (see table 2), over a period of several months, but did not usually reach the initial values. On daily ingestion of 6 gr., or more, the basal metabolic rate and the protein-precipitable iodine rose again (see figures 3, 4 and 5), and mild toxic symptoms were frequent; both factors then gradually declined but tended to become stabilized, often well above the control level, after several weeks, and

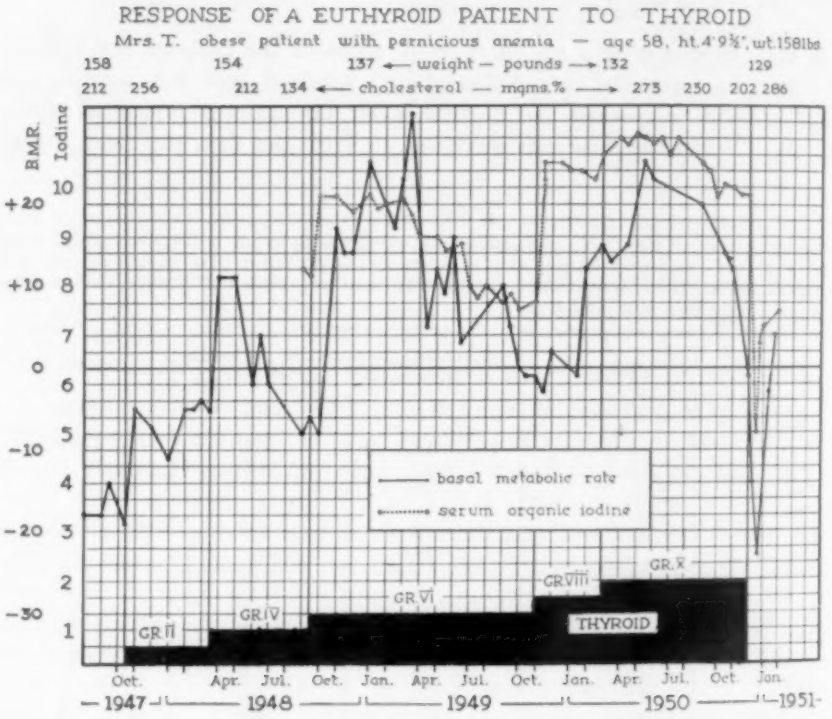
RESPONSE OF A EUTHYROID PATIENT TO THYROID
Mrs. T. obese patient with pernicious anemia — age 58, ht. 4' 9½", wt. 158 lbs.
158 154 137 ← weight — pounds → 132 129
212 256 212 134 ← cholesterol — mgms.% → 275 250 202 286
BMR. Iodine
+20 +10 0 −10 −20 −30
10 9 8 7 6 5 4 3 2 1
basal metabolic rate
serum organic iodine
GR. II
GR. IV
GR. VI
GR. VIII
GR. X
THYROID
Oct. Apr. Jul. Oct. Jan. Apr. Jul. Oct. Jan. Apr. Jul. Oct. Jan.
1947 1948 1949 1950 1951

Fig. 3. This patient had mild toxic symptoms at the beginning of the six grain dosage period, but they subsided later. Just at the end of the 10 grain period she was found to have a carcinoma of the stomach.

usually there was partial or complete relief of symptoms. On discontinuing administration of thyroid there was a rapid drop in the basal metabolic rate and the protein-precipitable iodine, with quick relief of any toxic symptoms present; the serum protein-precipitable iodine reached its lowest levels, definitely below the control values, in one to three weeks, and the basal metabolic rate about a week later. Both the basal metabolic rate and the protein precipitable iodine then rose gradually to the control levels in one or two months' time.

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There was great individual variation both in the *patients' tolerance* to the prolonged administration of increasing amounts of the drug and in the *response of the basal metabolic rate and protein-precipitable iodine.* One patient in the pre-war series suffered symptoms of hyperthyroidism on ingestion of only 3 gr. per day; she had tolerated 2 gr. well, her basal metabolic rate having risen to + 20 per cent, then fallen to the initial level of + 1 per cent; on 3 gr. per day, her basal rate rose to + 44 per cent and the drug had to be discontinued after three and a half months because of persistent heat

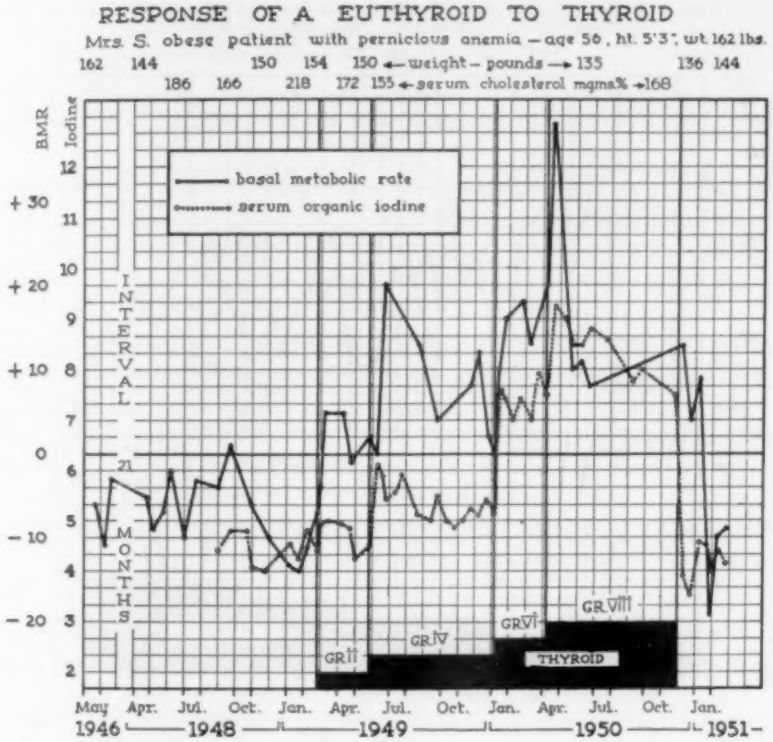

FIG. 4. This patient had very mild toxic symptoms on eight grains per day.

intolerance and other symptoms; her basal metabolic rate then fell quickly to — 14 per cent and the symptoms subsided. No other patient in either series suffered symptoms on so small a continued dose as 3 gr. On 4 gr. per day, however, Miss Z, an obese patient, had persistent mild symptoms because of which she ceased to take the thyroid, although she was losing weight; later, on an attempt to take 6 gr. per day, the symptoms quickly recurred and the thyroid was discontinued permanently. She was the exceptional case mentioned in the previous paragraph who, as shown in table 2, failed to acquire any tolerance to the drug; even on 2 gr. per day

the early rise in basal metabolic rate and protein-precipitable iodine was maintained and, with each subsequent 2 gr. increase, both factors rose in steplike fashion, with no decline on continued therapy; another unusual feature was that the actual increase in basal metabolic rate and protein-precipitable iodine was approximately the same with each increment in the dosage. Most of the other patients tolerated 4 gr. well; one, Mrs. R., showed little response in any way to 5 gr. per day (see table 1); she was

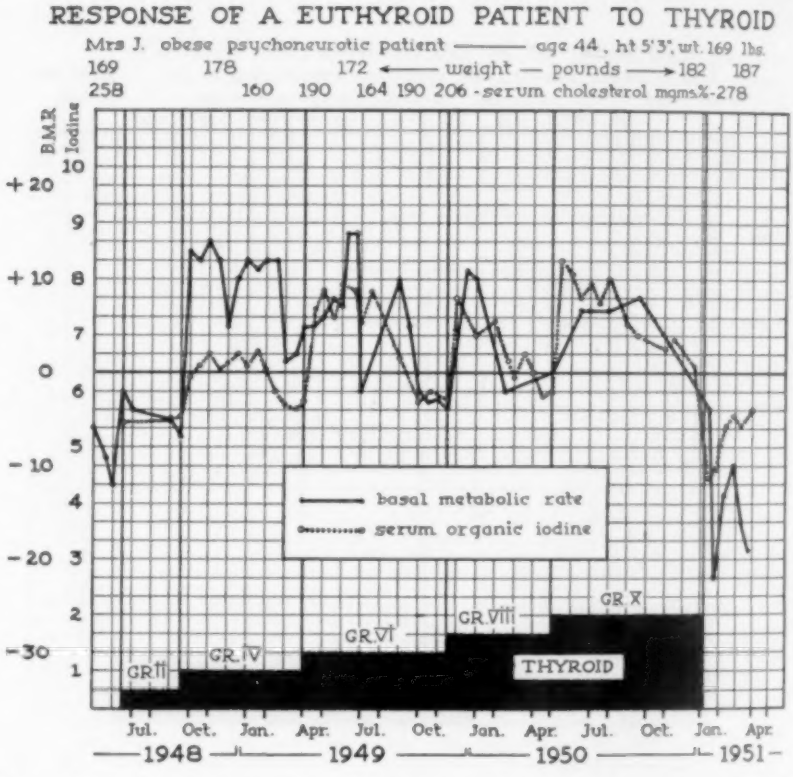

FIG. 5. This patient gained weight throughout and had no toxic symptoms. Note how small was the effect of high dosage on the basal metabolic rate and protein-precipitable iodine level.

very unresponsive. On 6 gr. per day, however, a number of patients began to lose weight and to suffer increased fatigue, mild malaise and palpitation, which symptoms decreased or subsided with continued administration; e.g., Mrs. T. (see figure 3). On the other hand, Mrs. J. (figure 5) was able to tolerate 10 gr. per day without distress; she actually gained weight while ingesting that amount. Her basal metabolic rate and serum protein-precipitable iodine reached approximately the same levels on 6 and 8 gr. as on 10 gr., and fell each time on continued therapy nearly to the control values.

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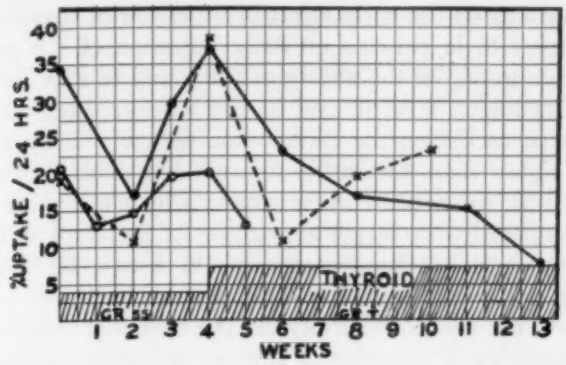

FIG. 6. The 24-hour thyroid uptake of radioiodine, expressed as percentage of the administered dose, during the early weeks of treatment with small amounts of thyroid.

In general, the level of serum protein-precipitable iodine roughly paralleled the basal metabolic rate. It rose more abruptly, however, whenever the dose was increased in the 2 gr. increments, reaching a peak in about two to three weeks' time, then fell more evenly, and did not present nearly as wide fluctuations as did the basal metabolic rate.

The serum cholesterol values, as indicated on the accompanying figures, changed little throughout; they tended to fall to lower levels during the administration of large amounts of thyroid, and the highest values were obtained immediately after discontinuing the thyroid. The variation when on a constant regimen was too great, however, for any reliance to be placed on individual figures.

At the beginning of this investigation, measurements of the thyroid uptake of radioiodine were not being made; in October, 1950, however, a

TABLE III

24-Hour Thyroid Uptake of Radioiodine in Patients Who Have Been Taking Different Amounts of Thyroid for Periods of Two Years or More

Patient	Thyroid, Daily Dose	Duration of Therapy	24-hour RaI Uptake
	Gr.	*Yr.*	%
M. R.	¾	18	16.5
M. J.	1	10	21.9 } Within the normal range.
A. Z.	2	10	15.3
M. B.	2	3	8.7 } Hypothyroid range, as
I. M.	3	6	9.3 } seen in moderately
L. A.	3	2	8.9 } severe anterior pituitary
L. B.	4	2	7.3 } insufficiency.
P. E.	4	5	4.8 } Myxedema and severe
S. P.	4	2	2.1 } anterior pituitary
B. F.	4	¾	1.5 } insufficiency range.
L. H.	5	3	4.5

series of observations on the early effect of ingestion of thyroid was begun. As shown in figure 6, in patients on daily ingestion of 0.5 gr. of thyroid there was a rapid decline in the ability of the gland to take up radioiodine, which reached its lowest level in one to two weeks; then, while the same amount was taken each day, the radioiodine uptake quickly rose to levels as high as, or higher than, the initial figure. On doubling the dose there was another decline, followed in some instances by a later rise. This same phenomenon was found when larger amounts—1.5 gr., 2 gr. and 3 gr.—were ingested each day. It has been noted also in a case of Graves' disease, when first 3 gr. and then 5 gr. of thyroid were given daily. As yet these observations have not been carried beyond the first four months of therapy.

After prolonged daily ingestion of thyroid in another group of patients,

TABLE IV

Recovery in Thyroid Function After Cessation of Ingestion of Large Amounts of Thyroid

Weeks after Cessation of Thyroid	24-Hour Thyroid Uptake of Radioiodine Expressed in Percentage of Administered Dose*		
	Mrs. S.	Mrs. J.	Mrs. T.
0	—	—	5.6
1	0.6	2.6	7.0
2	5	4	—
3	—	19	18
4	32	19	20
5	21	—	—
6	24	18	26
7	22	—	—

* 10–20 microcuries (free of carrier iodine).

the ability of the thyroid gland to take up radioiodine was found to vary considerably, as shown in table 3. It can be seen that the radioiodine uptake was not depressed below the normal range by ingestion of 1 gr., or less, per day. Of two patients on a dosage of 2 gr., the uptake was at the lower limit of the normal range in one and decidedly subnormal in the other. Prolonged ingestion of 3 gr. or more led in all cases to a greatly reduced uptake, often to myxedema levels.

The 24 hour radioiodine uptake of the three patients illustrated in figures 3, 4 and 5 was at myxedema levels just before cessation of thyroid therapy, and also one week later. In the succeeding two to three weeks, as shown in table 4, it rose to normal values. The glands appeared to have regained normal activity.*

* It should be pointed out that 10 gr. of Canadian Standard thyroid contain 1.8 mg. of iodine, and it is possible that this amount of iodine might reduce the 24-hour radioiodine uptake. Patients Mrs. S. and Mrs. J. (figures 4 and 5) are now being given 2 mg. of iodine per day as sodium iodide (April 5, 1951). The effect of this medication on the ability of the thyroid to take up radioactive iodine is being followed.

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Discussion

As noted in the earlier report,[1] prolonged ingestion of thyroid appears to put the patient's gland at rest. That even small doses affect its activity is indicated by the adjustment toward normal which follows the initial rise in basal metabolic rate (and protein-precipitable iodine) on continuation of thyroid therapy. (See figure 2.) Larger doses appear to have a more pronounced effect. (See table 3.) That the hypofunction may be associated with atrophy of the epithelium was shown in Cope's [2] patient with thyrotoxicosis factitia who was operated on as a case of Graves' disease. It is reasonable to postulate that the compensatory hypofunction and atrophy are due to failure of the thyroid gland to be stimulated by pituitary thyrotrophic hormone; the presence in the body of excess thyroid hormone might result in diminished production of thyrotrophic hormone or might render the thyroid epithelium less sensitive to its action; both mechanisms might be active. It is conceivable that a homeostatic mechanism in the thyroid gland may play a part in the regulation. That the depression of the thyroid gland is only temporary, however, is shown on cessation of treatment by the early return to normal of the protein-precipitable iodine, the basal metabolic rate and the ability of the thyroid gland to take up radioiodine, and by the subsequent clinical course of the patients.

There is a striking contrast between euthyroid and myxedematous patients in the response of their basal metabolic rate and serum protein-precipitable iodine to the prolonged ingestion of increasing amounts of thyroid. In patients with myxedema, the basal metabolic rate and the serum protein-precipitable iodine rise promptly in response to small doses of thyroid and remain elevated; on cessation of therapy, the basal metabolic rate falls off, rapidly at first, then slowly, reaching its ultimate low level only after two or three months. In euthyroid persons, on the other hand, the basal metabolic rate and serum protein-precipitable iodine are less affected by administration of small to moderate amounts of thyroid; instead of being maintained at a constant level, they tend to fall toward the control values; on cessation of therapy they both fall quickly, in one to three weeks, to subnormal levels, then gradually return to the original values within two to three months.

A comparison of the effect of large doses of thyroid in the two conditions cannot be made because large doses of thyroid were not given to myxedema patients after they had been stabilized in a euthyroid state. Most of our myxedema patients have been stabilized on 1.5 or 2 gr. per day. Some could not tolerate 2 gr. in the early months of treatment; severe symptoms have followed an increase to 3 gr. at this stage. One patient, maintained in health on 1.5 gr. daily for over a year, was unable even then to tolerate 3 gr. It seemed unjustifiable to go further. It is conceivable, however, that toleration for larger dosage [13] might be gradually acquired

by myxedema patients; but it seems likely, as suggested by P. E. Smith,[7] that the normal (i.e., euthyroid) organism is usually well buffered against excessive amounts of thyroid, whereas this buffering mechanism is less effective in thyroidless subjects.

The acquisition of tolerance in euthyroid patients on large doses of thyroid is associated with a gradual decrease in serum protein-precipitable iodine which is roughly paralleled by the basal metabolic rate. When the protein-precipitable iodine remained elevated, as in Miss Z. (table 2) or in Mrs. S., when she was taking 10 gr. of thyroid per day, the symptoms persisted. On the other hand, Mrs. J. presented no toxic manifestations at any time; whenever her thyroid medication was increased, even up to the 10 gr. level, the protein-precipitable iodine rose temporarily, but never above the upper limits of normal, and then soon fell off toward the control values. The mechanism that leads to tolerance appears to confer the ability to handle ingested thyroid in such a way that after the rapid rise in the serum protein-precipitable iodine curve, which follows each increase in dosage, there is a gradual decline. Whether this mechanism is a function of the thyroid gland or of other tissues, as in the case of the dog,[14] is a matter for conjecture. Our feeling is that the intact gland plays an important rôle in the regulation.

The tremendous variation in the response of the basal metabolic rate and serum protein-precipitable iodine to ingestion of varying amounts of thyroid is obvious from a study of the figures and tables presented. Similarly, the tolerance of different patients varied from inability to take 3 gr. per day without severe symptoms to complete tolerance of 10 gr. per day.

In clinical experience one is struck by the fact that, although all ranges of basal metabolic rate are found, from normal values to myxedema levels, the patients fall largely into two groups—euthyroid patients and those with myxedema. In the absence of clinical manifestations of myxedema, patients with grossly substandard rates are found to be really euthyroid: they usually have a normal serum protein-precipitable iodine; their 24 hour thyroid uptake of radioiodine lies within the normal range; if given thyroid in increasing amounts, they behave like euthyroid patients. The two groups are well separated by measurement of the radioiodine uptake. One finds only a small number of patients having a radioiodine uptake between the normal and the myxedema levels; *most* of these have moderately severe anterior pituitary insufficiency. With this exception, there appears to be an all-or-nothing principle: either the thyroid gland secretes enough hormone to keep the patient euthyroid or the patient is myxedematous. When the thyroid gland is largely destroyed or almost completely removed, the remaining portion either disappears, giving rise to myxedema, or increases in size under pituitary stimulation until normal function is regained.

It is interesting that the thyroid uptake of radioiodine in patients who have taken moderately large doses of thyroid (3 to 4 gr. per day) over long

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periods lies in the anterior pituitary insufficiency range; prolonged ingestion of smaller amounts leaves the uptake in the normal range, often at the lower limits; and ingestion of larger amounts lowers the uptake to myxedema levels. These observations lend support to the idea that the decreased activity of the thyroid gland under prolonged administration of thyroid is due to a decreased secretion of thyrotrophic hormone by the anterior pituitary.

Summary and Conclusions

1. The internal secretion of the thyroid gland may be greatly decreased and the gland reduced in activity and put at rest by the presence in the body of excessive amounts of its specific hormone.

2. Most euthyroid patients are able to acquire tolerance to the ingestion of large amounts of thyroid. Great individual variation is found, however, in the degree of tolerance attained: one patient took 10 gr. daily with impunity; another was unable to tolerate 3 gr. per day. The tolerance developed on a given large dose is associated with a gradual decrease in the serum protein-precipitable iodine and in the basal metabolic rate.

3. The ingestion of excessive amounts of thyroid hormone over a long period does not appear to affect the gland permanently. The depression is reversible and, after cessation of thyroid therapy, normal activity is soon regained.

Acknowledgment

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BLOOD PRESSURE VARIATIONS IN THE TWO ARMS *

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HEART disease and disease of the entire cardiovascular system are the causes of more disability and death than any other disease. Consequently, more and more attention is being directed to an evaluation of this system of the body. One of the simpler and more common tests in this evaluation is the checking of the blood pressure.

Determinations of blood pressure were made by Stephen Hales in 1733,[1] by direct readings on the open artery in large animals. The first attempt to measure arterial blood pressure in human beings is credited to Karl von Vierendt (1818–1884). Ludwig in 1847 published an article describing a "Kymographion" which produced tracings of the blood pressure of the open artery, and in 1876 Professor v. Basch of Vienna constructed a sphygmomanometer which made use of a fluid medium to obliterate the blood flow of the artery.[2]

It was not until after the turn of century that clinicians first began to take note of the significance of the blood pressure in relation to health and disease. Since that time, volumes have been written concerning it. Some of the data concern variations in results and interpretations according to the methods used,[3] diurnal and seasonal variations of blood pressure in the arm and thigh of man,[4] comparison of the blood pressure in the lying and standing positions,[5] and the effect of change of position of the arm upon the blood pressure.[6]

In 1939 a committee formulated standard methods for taking blood pressure readings. The types of instruments were discussed; the position of the patient, the position of the arm and the application of the cuff were standardized. It was also suggested that at the time of the first examination the blood pressure be checked in both arms, since it may not be the same.[7] In spite of this, very little has been written concerning the variation of the blood pressure in the right and left arms. A few references were found, such as a statement by Paul White in his textbook, "Heart Disease," that the blood pressure may vary in the two arms, and varies according to the size of the arteries, position of the arms and of the patient, and the state of contraction of the vessels.[8] Shock and Ogden found a statistically significant difference in the blood pressure of the two arms in half of the subjects they examined.[9]

Although clinically it may not be significant whether the blood pressure varies as much as 10 mm. of mercury, under many circumstances even this

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small difference may be of vital importance to the individual. This is particularly true in life insurance and employment examinations, and was significant in many cases in the Selective Service Act of 1940, where the upper limit of the systolic pressure was 150, and of the diastolic pressure, 90.[10]

Materials and Methods

In order further to evaluate this possible difference, a series of blood pressure readings was made in both arms of ambulatory patients seen in office practice. These patients were unselected except that those with aneurysms in the aorta or vessels supplying the upper extremities were eliminated. A standard method of taking the blood pressure was followed: The patients were in a sitting position, the same examiner made all of the tests, and efforts were made to eliminate the tension factors of variation which often occur between two successive readings in the same arm. This was accomplished by varying the arm used for the initial blood pressure reading; where the differences were marked, a recheck was made and the second set of readings was used. The same instrument, a Baumanometer, was used for all tests.

The statistics have been analyzed with regard to those patients with a known cardiovascular disorder and those considered normal. The upper limit for the normal blood pressure was considered as 140 systolic and 90 diastolic in the case of life insurance examinations, and as 150/90 in industrial and military examinations. All of the patients had a complete history, a physical examination and, where indicated, fluoroscopy of the heart and lungs as well as electrocardiograms. It was interesting, in analyzing the statistics, using the above figures as the upper limits, to note how many would have been accepted or rejected, depending on which arm was used to record the blood pressure, in the case of life insurance and employment examinations.

Results

A total of 755 consecutive patients were examined during the course of their regular office visit, and a total of 1,388 blood pressure readings were recorded on each arm of these patients. The cases were further analyzed as to the age groups, the number of patients with normal and abnormal cardiovascular systems, and the number having blood pressures highest in the right arm, the left arm, and equal in both arms. The degree of variation in systolic and diastolic readings was noted and has been tabulated in table 1.

It is interesting to note that the blood pressure was found to be highest in the right arm in 991 readings, as compared to 273 in the left arm, and to be equal in both arms in only 132 readings. The systolic variations in the two arms was 10 or more points in 694 readings, and zero to 10 points in 443 readings, out of the total of 1,388 tabulations. The diastolic variation in the two arms was much less marked, with 920 readings showing

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TABLE I

Tabulation of Results in 1,388 Blood Pressure Readings in 755 Patients

Number of Female Patients		Number of Male Patients		Age Groups in Years					
Normal cardio-vascular system	Abnormal cardio-vascular system	Normal cardio-vascular system	Abnormal cardio-vascular system	10–20	20–30	30–40	40–50	50–60	60+
263	548	219	358	36	146	261	328	331	286

Number with Right Arm Highest	Number with Left Arm Highest	Number with Both Arms Equal	Insurance Acceptable in One Arm Only	
			Complicated	Uncomplicated
992	274	122	33	132

Military and Industrial—Acceptable in One Arm Only	
Complicated	Uncomplicated
36	103

Variations in the Systolic Pressures in the Two Arms						Variations in the Diastolic Pressures in the Two Arms					
0–5	5–10	10–15	15–20	20–25	25+	0–5	5–10	10–15	15–20	20–25	25+
443	251	371	134	113	76	729	191	397	37	20	14

less than 10 points difference, as compared to 468 readings showing a difference of 10 or more points. The tabulation shows that, as the degree of variation of the blood pressure between the two arms increases, there is a reciprocal decrease in the number of cases. However, from these figures it can be seen that in more than half of the cases there is a significant systolic variation in the two arms, and in over one-third of the cases there is a significant diastolic variation.

In recording the effects of drugs, diet, surgery and other therapeutic measures on the blood pressure, it would be advisable to record the reading in both arms, or at least to use the same arm consistently in interpreting the results.

DISCUSSION

Life insurance companies, the military services and industry set certain minima of physical standards in accepting an individual. It is interesting to note what significance the recording of the blood pressure in both arms would have in this group of patients. The upper limit of normal, as previously stated, was accepted as 140 mm. of mercury systolic and 90 mm. of

mercury diastolic for life insurance, and a systolic of 10 points higher, with the same diastolic limit, for the military service and industry. It was noted that, of the 1,388 recordings, the difference in the blood pressure readings in the two arms in 165 instances would have made the difference between acceptance or rejection for insurance if only the blood pressure was considered, depending on which arm was used. In regard to the military service and to industrial employment, 139 cases would have been similarly affected by blood pressure differences in the arms if blood pressure were the sole criterion. These totals may not seem to be important statistically, but from the standpoint of the individual they can be of great significance. This discrepancy in the two arms may also help to answer the question as to why two observers get markedly different readings on the same patient.

Age was not a factor as far as blood pressure variations were concerned in those patients over 20. This series did not include enough cases under this age to warrant drawing any conclusions. Likewise, sex did not make any difference statistically. The presence or absence of cardiovascular disease was important only in that the degree of variation was greatest in the hypertensive group, as would have been expected.

This variation in the two arms is probably due to a number of factors, one of which is differences in the caliber of the arteries of the two arms. This was noted by Gross in at least two of the patients on whom he operated for coarctation of the aorta. In these the left subclavian artery was very small, producing a lower blood pressure in the left arm. Other causes may be external pressures on the vessels, atheromatous plaques and the state of contraction of the vessels. This latter condition may be responsible for that small percentage of the cases in which the highest pressure shifted from one arm to the other on different visits. These were cases in which the original difference was not great.

Summary

1. There is a significant incidence of variation in both the systolic and diastolic blood pressure in the two arms in patients with normal and abnormal cardiovascular systems.

2. The difference may be of vital importance to an individual in the case of examination for life insurance, employment or military service.

3. It is recommended that, at the time of the first examination of any individual, the blood pressure be taken in both arms and, if no significant difference is present, that the same arm be used consistently for follow up studies.

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THE USE OF VITAMIN B_{12} IN THE MANAGEMENT OF THE NEUROLOGIC MANIFESTATIONS OF DIABETES MELLITUS, WITH NOTES ON THE ADMINISTRATION OF MASSIVE DOSES *

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THE purpose of this paper is to report our experiences with the use of parenterally administered vitamin B_{12} in the management of 12 diabetic patients exhibiting unquestioned neurologic manifestations associated with the disease. We shall not discuss the features of so-called "diabetic neuropathy," other than for the corollaries necessary to our thesis. The reader interested in a detailed presentation of the subject is referred to the classical monograph of Rundles,[15] as well as to other excellent treatises available in the literature.[3, 14, 16]

Vitamin B_{12} has been found to arrest [6] and reverse [2] the neurologic changes in patients with pernicious anemia, and since the neurologic dysfunctions of the latter resemble in some respects those of diabetes mellitus, it appeared empirically possible that B_{12} might be of value in treating the neurologic manifestations of diabetes. An added stimulus was the fact that therapy with the previously known members of the vitamin B complex leaves much to be desired, and the evidence is scanty that such substances in themselves are effective beyond the pale of a prolonged, well-regulated diabetic regimen. The occasional appearance of such neurologic disturbances in patients whose diabetes has been closely followed and well-regulated within the limitations of our inadequate therapeutic knowledge likewise suggested the possible rôle of hitherto unknown factors.

We agree with Rundles [15] and with Karnosh [9] that the neurologic manifestations of diabetes may be an expression of a primary metabolic disturbance peculiar to the disease or the result of obliterative changes in the vasa nervorum, or a combination of both factors. We have adopted and modified the following classification of the neurologic manifestations of diabetes mellitus, as suggested by Karnosh [9]:

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The crystalline Vitamin B_{12} used in this study has been supplied by the following commercial houses: Merck & Co., Rahway, N. J., Squibb & Sons, New York, N. Y., and Eli Lilly & Co., Indianapolis, Indiana.

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A. Primary Diabetic Neuropathies
   1. Primary diabetic acroneuropathy
   2. Diabetic radiculopathy
   3. Diabetic pseudotabes
B. Diabetic Vascular Disorders
   1. Ischemic neuropathy
   2. Diabetic ischemic disease of the central nervous system
C. Autonomic Dysfunctions
   1. Loss of pilomotor control
   2. Sweating deficiencies
   3. Orthostatic hypotension and tachycardia
   4. Argyll-Robertson pupil
   5. Gastrointestinal dysfunctions
      a. Intermittent nocturnal diarrhea
      b. Constipation
   6. Sexual impotence
   7. Diabetic edema

Materials and Methods

To date we have treated 12 diabetic patients with neurologic disturbances for which no cause other than diabetes could be found, for periods varying between three and 13 months. Diabetics with subjective complaints only were not included, in order that evaluation of results might be as objective as possible. All patients had initially one or more of the following: absent or depressed patellar reflexes, unquestioned hypesthesias or paresthesias of the extremities, and ataxia, in addition to many of the other manifestations commonly encountered. Seven cases, later referred to as the "Long Term Group," were patients who had been observed between one and one-half and seven years, and who had had progressive neurologic lesions of six months' duration or more. Five of the subjects were followed in our Diabetes Clinic, and two were private patients of staff physicians who kindly made their observations available to us. Their diabetes had been well controlled and all had had intermittent courses of crude liver, yeast and the vitamin B complex without beneficial effects, a situation not uncommonly encountered by others.[15] The "Recent Group" comprises five patients whose diabetes was either newly discovered or neglected until included in this study. One member of this group was a private patient of a staff physician.

With the exceptions mentioned, all patients were seen at least weekly and in some instances daily by one of us, who likewise administered all medication throughout the entire course of observation. All patients were admitted to the hospital for initial observations, which included, in addition to history, physical and neurologic examinations, a complete hematologic examination, urinalysis, determinations of blood sugar, urea nitrogen, total

blood proteins and A/G ratio, a spinal fluid examination and gastric analysis. No patient had a history of syphilis, and all had two successive negative spinal fluid Wassermann and blood Kline and Wassermann reactions. These observations were repeated at suitable intervals during the course of treatment. None of the patients had pernicious anemia. In the case reports to follow the deep tendon reflexes are graded as follows:—absent; ± a faint quadriceps response but no movement of the leg; + a slight but definite movement of the leg; ++ a normal response; +++ hyperactive; ++++ marked hyperactivity approaching clonus.

All clinic patients were given daily saline injections for five to seven days prior to beginning treatment with B_{12}. In the majority of instances they were not informed of the object of therapy. Following a suitable period of observation in the hospital, patients were discharged to be followed in Diabetes Clinic. The more intelligent ones were able to keep a daily written log, noting any subjective changes in their course and any untoward occurrence in their daily lives.

The material employed was crystalline vitamin B_{12}, administered intramuscularly or subcutaneously. One patient (O.K.) was treated exclusively with streptomycin broth concentrate B_{12}. Adjusting dosage was at first largely a matter of trial and error, and because we did not have adequate

TABLE I

Relevant data in 12 diabetic patients with neurologic manifestations. Weight loss is considered as significant if immediately preceding or accompanying signs of neuropathy. Episodes of ketosis refer to those requiring hospital admission. Forty mg. per cent spinal fluid protein is considered high normal

Pt.	Age	Sex	Race	Duration Diabetes	Duration Neuropathy	Gastric Free HCl	HCl after Histamine	Diabetic Retinopathy	Recent Wt. Loss	Episodes Ketosis	Insulin Dosage	Initial Spinal Fluid Protein
"Long Term Group"												
W. B.	41	M	W	10 yrs.	5 yrs.	0	+	+	None	1	R.I. 70 PZI. 30	25 mg.
J. P.	33	M	W	14 yrs.	1 yr. and 6 mos.	0	+	+	None	1	R.I. 36 PZI. 6	70 mg.
F. C.	59	M	W	4 yrs	2 yrs.	0	+	+	None	0	PZI. 25	50 mg.
E. S.	34	M	W	9 yrs.	1 yr. and 6 mos.	0	0	+	None	3	PZI. 25	50 mg.
D. C.	65	F	N	6 yrs.	6 yrs.	0	+	+	None	0	R.I. 20 PZI. 20	100 mg.
Z. C.	66	F	W	16 yrs.	10 yrs.	?	?	+	None	?	PZI. 25	?
O. K.	60	M	W	10 yrs.	3 yrs.	?	?	+	None	0	PZI. 15	72 mg.
"Recent Group"												
J. C.	38	M	W	8 yrs.	3 yrs.	+	+	+	30 lbs.	5+	R.I. 130 to 26	120 mg.
L. A.	65	F	W	3 yrs.	6 mos.	0	0	+	30 lbs.	1	R.I. 46 PZI. 20	45 mg.
C. L.	39	M	N	3 yrs.	1 yr.	+	+	0	70 lbs.	2	Diet only	30 mg.
C. N.	77	M	W	10 yrs.	? 1 mo.	?	?	0	None	0	PZI. 12	96 mg.
M. P.	58	F	W	11 yrs.	1 yr.	0	+	+	None	0	PZI. 25	10 mg.

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TABLE II

"Long Term Group." Progress course while on B_{12} therapy

	W. B.		J. P.		F. C.		E. S.		D. C.		Z. C.		O. K.	
	Before B_{12}	After B_{12}	Before B_{12}	After B_{12}	Before B_{12}	After B_{12}	Before B_{12}	After B_{12}	Before B_{12}	After B_{12}	Before B_{12}	After B_{12}	Before B_{12}	After B_{12}
Paresthesias Upper extremities Lower extremities	None None	None None	None None	None None	None Severe (6 mos.)	None Remiss. Relapse Remiss.	None None	None None	Moder. Moder.	None Slight	None None	None None	None Moder.	None None
Hypesthesias Upper extremities Lower extremities	None Moder.	None None	None Slight	None None	Slight Moder.	None Slight	None Severe (18 mo.)	None None	Moder. Moder.	None Slight	None Moder.	None Moder.	None Moder.	None None
Temperature discrimination	Poor (low. ext.)	Normal	Mod. loss (low. ext.)	Norm.	Norm.	Norm.	Severe loss (low. ext.)	Norm.	Norm.	Norm.	Moder. loss (low. ext.)	Norm.	?	?
Ataxia	Moder. (5 yr.)	None	None	None	None	None	None	None	Slight	None	Slight	Slight	Moder.	None
Lightning pains, cramps (legs)	Moder. frequent	Slight infreq. (limited to toes)	None	None	Severe	None	None	None	Moder.	Slight (toes only)	Severe, frequent	Slight (toes only)	Moder.	None
Patellar reflexes	*Rt.* *Lt.* + − + −	*Rt.* *Lt.* + + + +	*Rt.* *Lt.* − − to to + − + −	*Rt.* *Lt.* + + + +	*Rt.* *Lt.* + − + −	*Rt.* *Lt.* + + + +	*Rt.* *Lt.* + + w/r	*Rt.* *Lt.* + + w/o/r	*Rt.* *Lt.* − −	*Rt.* *Lt.* + ?	*Rt.* *Lt.* ? ?	*Rt.* *Lt.* ? ?	*Rt.* *Lt.* − −	*Rt.* *Lt.* − +
Period of observation on B_{12} therapy	13 mos.		13 mos.		12 mos.		3 mos. and 2 wks.		9 mos.		8 mos.		2 mos. and 2 wks.	
Total B_{12} given*	885 y		825 y		750 y		630 y		1,140 y		1,400 y		450 y	

* In instances where individual test doses of 100 or 900 y were given, the amounts are not included in total (see text).

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TABLE II (*Cont'd*)

"Recent Group." Progress course while on B_{12} therapy. Data on patient J. C. omitted

	L. A.		C. L.		C. N.		M. P.	
	Before B_{12}	After B_{12}	Before B_{12}	After B_{12}	Before B_{12}	After B_{12}	Before B_{12}	After B_{12}
Paresthesias Upper extremities Lower extremities	 Moderate Moderate	 None Slight	 None None	 None None	 ? ?	 ? ?	 Moderate Moderate	 None None
Hypesthesias Upper extremities Lower extremities	 Moderate Moderate	 None None	 None None	 None None	 ? ?	 ? ?	 Moderate Moderate	 None Minimal (toes)
Temperature discrimination	Poor (lower ext.)	Normal	Normal	Normal	?	?	Normal	Normal
Ataxia	Acroataxia fingers	None	None	None	Severe	None	Moderate	None
Lightning pains, cramps (legs)	Moderate	Minimal (feet only)	None	None	Severe	None	Moderate	None
Patellar reflexes	*Rt.* *Lt.* − −	*Rt.* *Lt.* + +	*Rt.* *Lt.* +− +− w/r	*Rt.* *Lt.* + + w/o/r	*Rt.* *Lt.* − −	*Rt.* *Lt.* − −	*Rt.* *Lt.* + +	*Rt.* *Lt.* ++ ++
Period of observation on B_{12} therapy	12 mos.		6 mos.		1 mo.		4 mos.	
Total B_{12} given*	720 γ		645 γ		225 γ		540 γ	

* In instances where individual test doses of 1,000 or 900 γ were given, the amounts are not included in total (see text).

supplies of the material at the beginning, 15 y were given once weekly at the start of therapy. Added experience suggests a flexible schedule of 15 y to 30 y daily the first seven to 14 days, followed by a maintenance dosage of 15 y to 30 y once or twice weekly.

The following case histories present the salient features relevant to each patient. Pertinent details are summarized in tables 1 and 2. Estimations of vibratory sense have not been included in table 2. We have found this initially impaired in all patients, and it has been our impression that vibratory appreciation has improved in these patients during therapy. However, we could not be objective, since our tests were done with a hand tuning fork and the patients' response compared to that of the observer, rather than with an electrically driven tuning fork, such as was employed by Collens and associates.[2] The Achilles reflex has not been mentioned because, in our hands, it has been too variable and unreliable to subserve proper objectivity.

Case Reports

"Long Term Group"

Case 1. W. B., a white male, aged 41 years, had had diabetes of 10 years' duration. In 1944 atrophy of the lower legs appeared, with ataxia and drawing calf and plantar pains. He had severe paresthesias in both legs from 1942 to 1946, and had had marked constipation since 1946. Initial examination showed moderate ataxia with patellar reflexes ±; there was marked calf tenderness, and the patient complained of frequent and severe shooting calf and plantar pains. B_{12} was begun on July 22, 1949, in a dosage of 15 y once weekly intramuscularly. The calf pains and tenderness disappeared without recurrence after the first injection, and the ataxia disappeared by August 31. On September 28 the patellar reflexes were + bilaterally without reinforcement, and on November 2 they were ++ bilaterally without reinforcement. Constipation subsided after six weeks. The patient still complains of cramping of the soles of the feet and tingling of the toes, particularly at night, but they are less severe than was the case prior to therapy. At present, neurologic examination reveals no abnormality other than slight impairment of vibratory sense in both ankles. B_{12} has been continued in doses of 15 y weekly. In January, 1950, he developed intermittent claudication of both legs. Large doses of nicotinic acid were ineffectual in relieving symptoms, but maintenance therapy with Priscoline® improved exercise tolerance slightly. Two spinal anesthetics at weekly intervals improved exercise tolerance and eliminated plantar cramps and pains for two days on each occasion, although dermatherm readings indicated no change in skin temperature.

Comment: Recovery from ataxia has been this patient's most notable result. Prior to therapy with B_{12}, he had been greatly embarrassed because passers-by mistook his staggering gait for drunkenness.

Case 2. J. P., a white male, aged 33 years, had had diabetes for 14 years. Severe constipation had been present for one and one-half years. Initial examination disclosed moderate loss of heat and cold discrimination of the legs, with slight loss of vibratory sense at the ankles. The patellar reflexes were − to ± bilaterally. B_{12} was begun on July 28, 1949, in a dosage of 15 y once weekly. The constipation disappeared after the first injection and has not recurred. By October 27 all sensory

disturbances were greatly diminished, and the patellar reflexes were ++ without reinforcement. By April 28, 1950, neurologic examination was entirely normal and vibratory sense appeared grossly normal. On July 14, an episode of bronchopneumonia necessitated admission to the hospital. At this time the blood urea nitrogen was found consistently elevated, and there is now a constant albuminuria. In spite of the evidence of intercapillary glomerulosclerosis, there are no neurologic abnormalities and the patient remains asymptomatic.

Comment: Chronic constipation had been this patient's most distressing complaint. Relief has been dramatic and lasting.

Case 3. F. C., a white male, aged 59 years, had had known diabetes for four years. For the past two years the skin of the lower extremities had been dry and scaly, and there had been absent palmar sweating. There had been numbness, aching and cramping of the calves, chiefly at night, and shooting pains in the medial aspect of the thighs for the past 18 months. The patient had been unable to cross his legs because of severe burning paresthesias and hyperesthesia for the past six months. Initial examination disclosed the above findings and patchy hypesthesia to pinprick of the lower legs, with slight loss of vibratory sense at the ankles. The patellar reflexes were ± with reinforcement. B_{12} was begun on August 12, 1949, in a dosage of 15 γ once weekly. After the second injection the paresthesias and hyperesthesia disappeared completely. On October 22 the sensory examination was normal and the patellar reflexes were ++ without reinforcement. On December 15 the patient developed recurrent, steady, severe pain in the medial aspect of both thighs. Large doses of thiamin chloride were added to B_{12} on January 4, 1950, without noticeable effect. On February 8, medial thigh pain became much more severe, and there was a recurrence of burning paresthesias about the low back, abdomen and thighs, and hyperesthesia of the thighs. These subjective complaints were not as severe as they had been prior to treatment; shooting and cramping leg pains did not recur and the reflexes remained normal. On March 24, B_{12} and thiamin were discontinued and a 15 day course of BAL,[5] 150 mg. daily, was begun with relief of the paresthesias, although the steady medial thigh pain persisted. By June 7, approximately 10 weeks after discontinuance of B_{12} therapy, there was recurrent hypesthesia to pinprick in the lower legs, with occasional cramps and stinging pains in the left calf and toes of the left foot at rest. B_{12} was again started on this date, and there has been prompt abatement of shooting pains. At present (August 9, 1950), the neurologic examination is again completely negative. The patient's only complaints are steady dull pain along the medial aspect of the left knee and a burning sensation about the hips, noticed only when sitting down. However, there are no abnormalities of skin sensation in these areas.

Comment: This patient has in addition to his diabetic neuropathy spondylarthritis and generalized arteriosclerosis. The former may be responsible for the positional paresthesia. At the time that the patient suffered a recurrence of paresthesias and hyperesthesia while on combined B_{12} and thiamin therapy, the spinal fluid protein rose from a previous normal of 35 mg. per cent (October 20, 1949) to 90 mg. per cent (March 16, 1950). Following completion of BAL therapy, in spite of complete relief of paresthesias, the spinal fluid protein rose to 100 mg. per cent (April 7, 1950). At present, while the patient is on B_{12} therapy only and virtually asymptomatic, it has resumed normal levels (30 mg. per cent on August 2, 1950).

The significant consideration is the recurrence of shooting pains upon

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discontinuance of B_{12}. It is also of interest that this is the only patient who so far has shown a significant partial relapse while under therapy. This occurred while he was being given large doses of thiamin intramuscularly.

Case 4. E. S., a white male, aged 34 years, had been a known diabetic for the past nine years and had had several bouts of acidosis. An amputation of the right great toe was done in 1946 because of osteomyelitis due to occlusive vascular disease. Since April, 1949, he had exhibited the clinical picture of intercapillary glomerulosclerosis with pedal edema, albuminuria, hypoproteinemia, hypertension and anemia, and a blood urea nitrogen of 50 mg. per cent. Definite loss of heat and cold discrimination, with marked hypesthesia below the knees, developed one and one-half years prior to admission. About September 23, 1949, the patient developed intermittent nocturnal diarrhea and on October 10 was admitted to the hospital. At this time the patellar reflexes were ± without and + with reinforcement. Following a satisfactory insulin and dietary control period of 14 days, during which time the patient showed no change in neurologic signs, B_{12} therapy was begun on October 25. The patient was given 15 γ daily for the first 16 days. The dosage was then reduced to 15 γ three times weekly for two weeks, and subsequently to 15 γ twice weekly. After the second injection of B_{12} all sensory disturbances cleared completely, and after the seventh injection there was complete abeyance of the diarrhea. The latter never recurred. The patellar reflexes became + without reinforcement. There was no return of neurologic complaints, in spite of severe recurrent furunculosis, edema and persistent azotemia. On February 4, 1950, B_{12} was discontinued. He was readmitted to the hospital on February 19 because of severe edema and uremia, but until death there was no recurrence of the original neurologic symptoms. On February 28 he suffered the first of several cerebrovascular accidents and died in coma on March 4. Permission for necropsy was refused. This patient never required more than 25 units of P.Z.I. daily in order to maintain the blood sugar level at about 150 mg. per cent.

Comment: This subject had a chronic normocytic anemia, with a red blood cell count in the neighborhood of 2.5 million, consistent with the presence of severe chronic renal disease. The bone marrow was hyperplastic and the red count could be maintained only by means of repeated transfusions.

Case 5. D. C., a Negro female, aged 65 years, was first discovered to have diabetes in 1944 during a hospital admission for a right rectolumbar abscess. At the same time the patient developed intermittent numbness and paresthesias of the fourth and fifth fingers of both hands, of the toes and of the dorsal aspect of the feet, and cramping pains of the calves and the soles of the feet, worse at night. Initial examination disclosed quasi Argyll-Robertson pupils, diminished vibratory sense below the knees, a slight but definite ataxia to the right and totally absent patellar reflexes. B_{12} was begun on November 1, 1949, in a dosage of 15 γ twice weekly. All sensory disturbances were gone from the fingers after the second injection; all symptoms in the legs and feet became greatly diminished in intensity and frequency. On December 21 the right patellar reflex was + and the left still − with reinforcement. On March 8, 1950, a left mid-thigh amputation was performed because of gangrene and osteomyelitis of the foot. In spite of this, improvement has been sustained. Treatment is being continued.

Comment: This patient's only residua consist of occasional slight and transient numbness and twinges of pain, limited to the toes and accompanied by minimal hypesthesia. Vibratory sense appreciation appears somewhat improved in the remaining leg.

Case 6. Z. C.,* a white female, aged 66 years, had been a known diabetic for 16 years. The patient was well controlled and had been followed closely by her private physician for a number of years, and during that time she was given the usual supportive vitamin therapy. In spite of this, there developed hypesthesia of the feet of 10 years' duration, subjective coldness of the feet of five years' duration, and frequent lancinating pains in the legs and toes during the past three years. In December, 1949, she was treated successfully with penicillin for osteomyelitis of the right great toe. At that time there were definite hypesthesia of both feet, some ataxia of the lower extremities and impairment of vibratory sensation over the iliac crests and lower extremities. B_{12} was given in a dosage of 20 γ daily for two weeks in January, 1950, and maintenance dosage of 20 γ twice weekly has been continued since. Following the first few doses of B_{12}, the shooting pains dramatically decreased in frequency and intensity. Improvement has been sustained and treatment is being continued.

Comment: Previous to therapy with B_{12}, shooting pains had been so severe as to interfere with this patient's physical activity. She now has only minimal twinges, not oftener than once weekly.

Case 7. O. K.,† a white male, aged 60 years, had diabetes of 10 years' duration, well controlled since 1942. Examination on March 1, 1947, following the complaint of shooting leg pains of two months' duration, revealed—patellar reflexes present even with reinforcement, and marked diminution of vibratory and pain sensation over both legs. He was treated with parenteral thiamin, 25 mg. twice weekly, and oral B Complex daily. On August 11 there was slight improvement in the altered sensory modalities, and the leg pains had decreased moderately in frequency and severity. In December, 1949, he developed paresthesias and numbness of both feet, weakness of both legs and painful big toes. He was admitted to the hospital on May 29, 1950, for evaluation. There were hypesthesia bilaterally over the dorsa of both feet,—patellar reflexes even with reinforcement, and a positive Romberg sign. The feet felt subjectively cold and were anhidrotic. Vitamin B_{12}, in a dosage of 15 γ daily, was started on May 30. On the second day of treatment the area of hypesthesia on the dorsum of the right foot was reduced and the Romberg had become negative; on the third day perspiration returned to the feet; on the fourth day the patient noticed decrease in the shooting pains of the toes, the left patellar reflex was + without reinforcement, and only a small zone of hypesthesia remained on the dorsum of the left foot, the feet feeling warm and moist; on the fifth day both legs felt subjectively stronger, paresthesias had disappeared and the only sensory abnormality was a 3 by 3 cm. zone of hypesthesia on the dorsum of the right foot, which gradually decreased by the seventh day to 1 by 2 cm. He was discharged on June 7 and placed on B_{12}, 15 γ three times weekly, reduced to twice weekly on July 3. The patellar reflex has remained absent on the right and has been transiently absent and + on the left. A small zone of hypesthesia over the dorsum of the right foot and the right big toe remains; otherwise the neurologic examination at present is subjectively and objectively normal.

* For the clinical data in this case we are indebted to Dr. E. E. Beard.
† For the clinical data in this case we are indebted to Dr. E. M. Chester.

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Comment: As in the previously described cases, the only alteration in therapy was the addition of vitamin B_{12} to the regimen.

"Recent Group"

Case 1. L. A., a white female, aged 65 years, had diabetes of three years' duration. In the six months prior to admission, the patient developed paresthesias of the fingers and toes, marked acroataxia of the fingers (unable to lace shoes), and a recent profound weakness of the lower extremities. Initial physical examination disclosed these findings and, in addition, Argyll-Robertson pupils, diminished vibratory sense below the knees, and patellar reflexes which were absent with reinforcement. No changes in neurologic signs were noted after one week of proper diabetic control. B_{12} was begun on August 22, 1949, and after receiving 15 γ daily for four days, dosage was changed to 15 γ once weekly. On September 14 the fingers were almost normal, and the patellar reflexes were ± with reinforcement. On December 21 the patellar reflexes were + with and without reinforcement. Cramps in the calves and feet became minimal after the first two injections of B_{12}, and since April, 1950, there have been no sensory complaints other than slight cramps in the soles of the feet, particularly at night. At present the only objective neurologic abnormalities consist of patellar reflexes which are + bilaterally, and a slight diminution in vibratory sense appreciation at the knees and ankles. Treatment is being continued.

Comment: This patient has a histamine refractory achlorhydria, but pernicious anemia was ruled out on admission by the presence of a red blood cell count of 4,000,000, hemoglobin of 12 gm., MCV of 89 and a normal bone marrow.

Case 2. C. L., a Negro male, aged 39 years, had had known diabetes since 1947, when he was admitted because of periurethral abscess and ketosis. The patient did not follow dietary and insulin therapy, with a resultant weight loss of 70 pounds. One year prior to the present admission impotence developed, and four months prior to admission persistent intermittent nocturnal diarrhea appeared. On initial examination the only abnormal finding was the presence of ± patellar reflexes with reinforcement bilaterally. Diabetes was controlled on diet alone. B_{12} was begun on November 18, 1949, and by December 31 the patient had received a total of 390 γ, without improvement of the diarrhea, although the patellar reflexes were now definitely +. Thiamin chloride, in the dosage of 100 mg. intramuscularly twice weekly, was added on December 31. By March 28, 1950, all gastrointestinal symptoms had gradually subsided, but it is questionable that such abatement of symptoms was due to other than proper dietary control of the diabetes. Libido and normal potency returned by April 15, but, possibly due to unexpected improvement in that feature of his disease which was to him of greater concern, the patient failed to return and we have been unable to follow him.

Case 3. C. N.,* a white male, aged 77 years, had been a known and uncontrolled diabetic for 10 years. The patient was admitted to the hospital on November 6, 1949, because of severe staggering of several weeks' duration. There was no ketosis. Initial examination revealed severe ataxia, staggering gait and a markedly positive Romberg sign. The patellar reflexes were absent with reinforcement; sensory evaluation was difficult because the patient was deaf. The spinal fluid protein was 96 mg. per cent. The diabetes was controlled rapidly on less than 20 units of P.Z.I. daily. There was no change in neurologic signs after five days. B_{12} therapy was begun on November 11, 1949, in a dosage of 15 γ daily. After the third injection

* For the clinical data in this case, we are indebted to Dr. E. M. Chester.

the gait started to improve. On November 18 the patient was discharged from the hospital, and B_{12} was given in a dosage of 15 γ twice weekly intramuscularly. On November 21 the Romberg was completely negative. On December 5 the patient was able to cross his legs, which he had been unable to do previously because of pain. B_{12} was permanently discontinued on December 12. At this writing (August 15, 1950), the patient requires only 12 units P.Z.I. daily. The patellar reflexes have remained absent; improvement has been sustained.

Comment: The persistence of improvement in this patient eight months after discontinuance of B_{12} therapy is of interest, in view of the observations on the next patient to be presented.

Case 4. M. P., a white female, aged 58 years, had been a known diabetic for 11 years, carefully controlled (except for the last six months) in another hospital on diet and maximal insulin dosage of P.Z.I. 25 units. There were three previous admissions to another hospital between 1947 and 1949 because of congestive failure due to hypertensive and coronary artery heart disease. There had never been ketosis. She was admitted to Cleveland City Hospital on March 22, 1950. Control of the diabetes had been poor in the preceding six months because of inauspicious family circumstances. There were numbness and tingling of the finger tips and toes, shooting leg pains of one year's duration, and a moderate right hemiparesis of three weeks' duration. Neurologic examination on March 22 revealed, in addition, a band of hypesthesia to pinprick on the anterior abdomen between the levels of T10 and T12, and a similar disturbance from the knees down. There was numbness of the fingertips of the left hand, and the patellar reflexes were + with and without reinforcement. There was complete loss of vibratory sense at the malleoli of both ankles. Control of the diabetes was quickly effected with diet and insulin. On April 16 the patellar reflexes were still +, and there were persistent numbness and tingling of the fingertips of the left hand and hypesthesia of the medial aspect of both legs. B_{12} was started in a dosage of 15 γ daily and was continued for nine days. By the second day of treatment the numbness and tingling in the fingers had disappeared. On the third day the patellar reflexes were ++. On the ninth day the neurologic examination was completely negative except for slight numbness and hypesthesia to pinprick of the feet and toes; vibratory sense had returned, though impaired, to both ankles. Other than for the purposely induced neurologic relapses to be described, the patient has been comfortable, well controlled and ambulatory about the ward until a recent episode of pulmonary infarction. The patient is homeless, and her enforced hospital stay in the past four months has afforded opportunity for very closely conducted daily observations.

On April 15, B_{12} was discontinued and daily hypodermic administration of sterile saline was begun. By May 26, formications returned in both feet, together with now definite hypesthesia to pinprick of both feet; there was recurrent loss of vibratory sense at the left ankle. By June 11 the patient was unable to fall asleep because of pedal formications and an annoying subjective numbness of the feet. On June 12, B_{12}, 15 γ daily, was substituted for the saline injections. By the fourth day of therapy, pedal formication and subjective numbness had disappeared. By the ninth day of therapy there was slight but definite return of vibratory sense to the left ankle and only slight hypesthesia to pinprick of the feet. Sterile saline injection was again begun. On the third day, vibratory sense was again absent at the ankles and hypesthesia of the feet increased. On the sixth day, there was complete hypesthesia of both feet (able to draw blood with a pin without sensory appreciation) and also recurrent subjective numbness of the feet. Another nine-day course of B_{12} again reversed these findings, and by the ninth day the neurologic examination was com-

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pletely normal. On July 5 the patient complained of pain and tenderness in the right calf, not relieved by a single injection of 900 y of B_{12}. Two days later a pulmonary infarction occurred, and calf pain and tenderness abated completely four days after the inception of anticoagulant therapy. After 22 more days of saline injections, the patellar reflexes were + with reinforcement. There were hypesthesia to pin prick below the knees, slight tingling of the feet, subjective numbness of the feet and greatly impaired vibratory sense at the ankles. On July 27 another single dose of 900 y of B_{12} was given. Improvement began promptly, as expected, but stopped incompletely after three days. On August 1, B_{12}, 15 y daily, was again started, and at this writing (August 12), neurologic examination is again completely negative (patellar reflexes ++) except for moderate impairment of vibratory sense at the ankles.

Comment: This patient has required frequent administration of B_{12} to maintain a neurologic remission. This may be related to the severe atherosclerosis, clinically evident in absent dorsalis pedis pulsations, poor skin temperature response to environmental room temperature changes (vide infra), calcification of leg vessels, severe diabetic retinopathy and retinitis proliferans to the point of near-blindness. In addition, there is intercapillary glomerulosclerosis, as evidenced by chronic normocytic anemia, hypoproteinemia, albuminuria and chronic azotemia (blood urea nitrogen constantly between 40 and 60 mg. per cent in the past four months). Her "neuropathy" is probably the result of a combination of primary metabolic and vascular factors, the former predominating and being at present reversible. It is interesting that each time B_{12} was discontinued the integrity of various modalities was lost in a similar pattern: vibratory sense, vital sense (hypesthesia to pinprick and paresthesias), gnostic sense (subjective feeling of numbness) and patellar reflexes; and recovery followed in the reverse direction on resumption of treatment. Lancinating pains and disturbances in the upper extremities have never recurred.

The Use of Massive Doses of B_{12}

Concentrations of B_{12} in the order of 1,000 y and 900 y per c.c. were made available to us by Merck & Co. These we employed variously, as noted above, and to test the possibility that the drug may have nonspecific effects (see below). In patient M. P. the administration of 900 y gave results similar to the administration of 15 y. Patients W. B. and D. C., whose only residual symptoms consist of occasional pain in the feet and toes at night, were given daily injections of 900 y each for five days. In neither instance were these minor symptoms relieved. It is of interest that on two separate occasions the plantar cramps in W. B. were totally ablated for two days by a spinal anesthetic.

The opportunity for a thorough trial of massive amounts of B_{12} arose in patient J. C. This subject was the only member of the entire group who had proved refractory to therapy and, in addition, he had been a chronic alcoholic to the time of admission, when he was brought to the hospital in

mild ketosis, severely malnourished and at the climax of a prolonged alcoholic spree.

Case 5. J. C.,* a white male, aged 38 years, had had diabetes for about eight years. The patient was uncontrolled most of the time. Three years before admission he developed loss of libido. Impotence supervened four months before admission. Initial examination revealed absent patellar reflexes, loss of temperature discrimination below the knees, and patchy hypesthesia to pinprick below the knees. There were severe leg cramps. The spinal fluid protein was persistently elevated above 100 mg. per cent. The patient was given a total of 300 γ of B_{12} from July 23 to October 8, 1949. Following the initial injection there was at first a disappearance of the shooting leg pains. These recurred, though less severely than initially, during B_{12} therapy, and he developed increasing hypesthesia of the legs. Daily injections of massive doses of vitamin B complex were begun on October 13, and discontinued on November 1, when the patient was placed on crude liver, orally and parenterally, daily until November 23. At this time there developed absence of all deep tendon reflexes, complete hypesthesia to pinprick below the knees with loss of vibratory sense, and a recurrence of violent and excruciating leg pains, requiring codeine for palliation.

During this period we attempted unsuccessfully to regulate the blood sugar by various mixtures of regular and protamine zinc insulins, but it now became apparent that we were dealing with a "brittle" diabetic. He was placed on four daily doses of regular insulin totaling 130 units a day. A satisfactory control was attained, and by February 15, 1950, he had regained 30 pounds, to his sustained present normal weight of 145 pounds. On this date he was readmitted to the hospital for controlled observations. Neurologic examination revealed a return of the deep tendon reflexes, though totally absent patellar responses, patchy hypesthesia and loss of temperature discrimination involving 80 per cent of the skin surface below the knees (four weeks before, he had suffered second degree burns of both feet from a hot water bottle), and a positive Romberg sign with moderate ataxia; vibratory perception was moderately impaired. Subjectively, he complained of numbness and tingling of the fingers and toes ("they feel as though they were made out of wood"), and of severe, frequent lancinating leg pains and a constant "heavy" feeling in the legs. The spinal fluid protein was 90 mg. per cent. On February 16, B_{12} in a dosage of 15 γ daily was started and continued for seven days. The only induced change was a slight decrease in the intensity of the leg pains. On February 23 he was given the first of 10 1,000 γ doses, which were administered every other day until March 13. There was a dramatic and persistent cessation of all shooting pains, and for the first time in 10 months of observation the patellar reflexes became ±. By the termination of this course the patient estimated an 80 per cent improvement in the subjective feeling of acral numbness, most of the improvement having occurred by the fifth dose. Vibratory sensation and temperature discrimination became almost normal, but hypesthesia remained unchanged. In spite of the obvious improvement, the spinal fluid protein was now 85 mg. per cent.

On March 14, B_{12} therapy was discontinued. Three days later he noticed a recurrent heaviness and dull pains in the legs; eight days later severe tiredness of the legs developed; 10 days later sharp, shooting leg pains recurred with the same previous intensity and frequency, and the patellar reflexes were again absent. The other improvements noted were sustained. On April 6 another similar course of B_{12}, 1,000 γ every other day, was administered, terminating on April 26. The clinical course duplicated the previous experience. The spinal fluid protein was 80 mg. per

* The relevant data in this case are excluded from table 2.

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cent at the beginning and, strangely enough, 120 mg. per cent at the end of this 20 day period, in spite of obvious improvement.*

There were now only small patchy areas of hypesthesia over the lower legs. No B_{12} was administered until June 7, at which time he complained of mild subjective numbness of the toes and shooting leg pains of moderate intensity and frequency. For three weeks he was given 1,000 γ once weekly; each time the leg pains recurred on the fifth day following each dose. On June 28, dosage was reduced to 15 γ weekly, which is being continued to date. He is now free of pain except for dull aches which occur on the sixth day after each injection. The patellar reflexes are +, with and without reinforcement; temperature discrimination in the legs is normal; vibratory sense is slightly impaired over the ankles; there is minimal residual acrodysesthesia of the toes, and a few dime-sized areas of hypesthesia are still present in the lower legs. The spinal fluid protein is now 60 mg. per cent (August 10, 1950), and insulin requirement has dropped gradually to 26 units daily.

Comment: It is of interest that improvement began only when a satisfactory control of the blood sugar had been attained. It is probable that the overall improvement was the result of the gradual amelioration of the diabetic state per se, but it is unquestioned that certain modalities were specifically affected by B_{12}. It is doubtful that such enormous doses as were used were required. The minimal dosage effective in eliminating pain, his most distressing complaint, was not determined.

Our conclusion at present is that massive dosage of B_{12} may be indicated in the exceptional patient showing severe manifestations, but it is doubtful that improvement can be attained more quickly and any more completely than with the usual small doses.

Discussion

None of the conditions often associated with the diabetic state, other than the neurologic manifestations, has been affected by vitamin B_{12} administration. All subjects except two have slight to moderate diabetic retinopathy, which has not noticeably changed during the period of observation. In one patient (M.P.), retinopathy has progressed to the point of near-blindness, while the neurologic disturbances have disappeared. There has been no relation between the presence or absence of histamine achlorhydria, symptomatology, past and present course of the disease, and clinical response while on B_{12} therapy. Seven of the nine patients in whom gastric analysis was done had an absence of free hydrochloric acid, but only one had a histamine achlorhydria. The occurrence of achlorhydria in diabetics is not uncommon,[12] and no conclusions can be derived therefrom. Intercapillary glomerulosclerosis has shown clinical progression in two patients (E. S., M.P.), and one patient (J. P.) developed the first objective signs of the disease some months after B_{12} therapy was initiated, even though at present he has no complaints and the neurologic examination is normal. Hemograms have remained unchanged; one patient with a severe

*A similar experience has been noted in patients with diabetic "neuropathy" treated with BAL, which appears effective mainly in relieving such individuals of paresthesias.[10]

"renal" anemia required frequent transfusions, and the mild anemias present in some of the other patients remained unchanged. A lumbar puncture was done in all subjects except one, and the protein was found to be elevated beyond the normal in eight. In six of these it was possible to do frequent examinations: in four, values have fallen to normal or near normal, and in two they have increased in spite of clinical improvement. It is of interest that in all instances the gum mastic test has been negative; Tiselius partition studies on blood and spinal fluid proteins, were it possible to conduct such studies on the latter, before and after B_{12} administration may yield additional information. The abnormal texture of the skin often present in these patients has remained unchanged. We have not been impressed by any subjective feeling of wellbeing following the use of B_{12}, other than the mental relief and improved outlook on the part of the patient relieved of pain or annoying dysesthesias.

Our experience in regard to the abatement of cramping and lightning calf and plantar pain has been somewhat similar to that of Bean and associates [1] in their acute experiments in which B_{12} was given to patients with painful neuropathies of varied etiology. There has been a rapid initial disappearance of pain, but occasionally after several weeks it has recurred, although invariably much less in frequency and severity. Totally absent patellar reflexes have at times been restored and, when initially hypoactive, have resumed a normal response. Paresthesias, as well as various subjective dysesthesias, have disappeared, and temperature discrimination has returned to normal. Hypesthesias have disappeared, although the response here has been variable and slower than that of the other modalities. It is our impression that vibratory sense appreciation has improved, although by the crude estimation possible with a hand tuning fork we cannot be strictly objective. With few exceptions, we believe that there has not been a complete return to normal.

The entire neurologic picture and the response to treatment with B_{12}, other vitamins and regulation of the diabetic state, insofar as is possible within the limitations of our therapeutic knowledge, are clouded by the at least double etiology of these manifestations. Indeed, it is difficult to separate the effects of primary nervous tissue degeneration from those secondary to intrinsic sclerotic and proliferative lesions of the vasa nervorum in evaluation of the final clinical picture. Woltman and Wilder [16] have shown histologically that such lesions occur in the vasa nervorum of diabetics, leading to secondary nerve degeneration, and Roberts [13] has reproduced these lesions experimentally in animals. Presumably such lesions would be pathologically and physiologically irreversible. Our three female patients, all of whom had numbness and tingling of the hands, feet and toes in addition to calf and plantar cramps, noticed a complete remission of symptoms in the hands, but only a partial remission in those complaints referable to the lower extremities. One might speculate that the latter are partly due to vascular

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FIG. 1. Cross section of small perineural artery, posterior tibial nerve. There is thickening of the media and intima with intimal degeneration. (H. & E. stain. Photomicrograph, magnification × 150.)

changes, which are usually more pronounced in the legs and feet and probably irreversible.

Evidence supporting this view is afforded by the histologic changes in the posterior tibial nerve in the amputated leg of D. C., which showed extensive hyalinization and thickening of the media of the arterioles intrinsic to the nerve bundles, and some proliferation of the intima in both arterioles and small arteries. Resorcin-fuchsin stains were poor because of technical

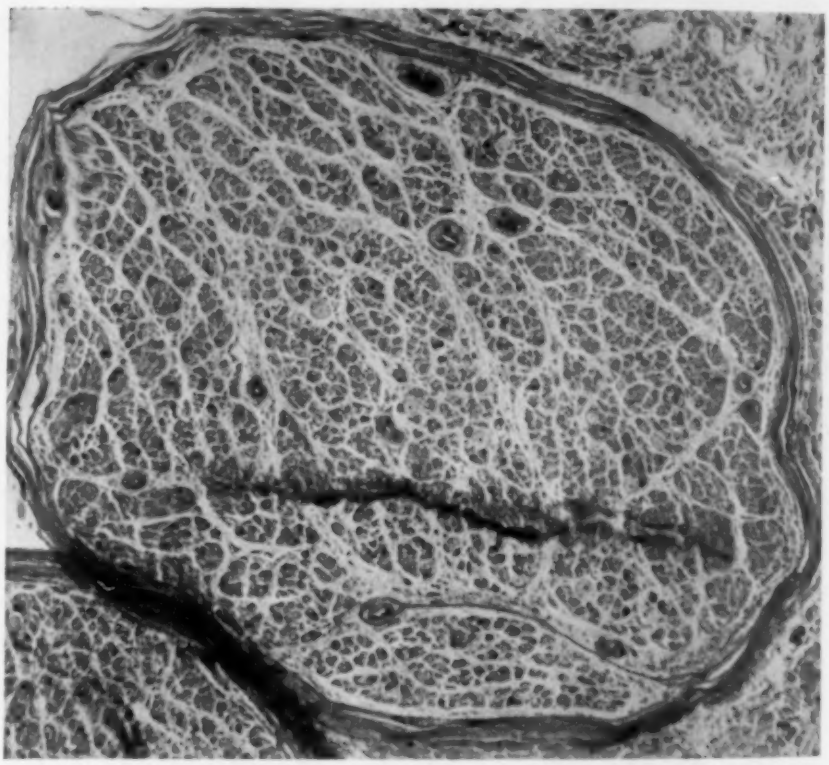

FIG. 2. Cross section of nerve bundle within posterior tibial nerve. The thickened intrinsic arterioles are readily seen; degenerated nerve fibers are also noted. (H. & E. stain. Photomicrograph, magnification × 125.)

difficulties, but the myelin sheaths appeared mostly intact in the hematoxylin and eosin preparations (figures 1, 2 and 3).

Both patients E. S. and C. L., with intermittent nocturnal diarrhea, presented clear roentgenologic evidence of marked gastric and intestinal atony, as previously described by Hodges and associates.[7] It is of interest that E. S., who had a chronic azotemia, peripheral arteriosclerosis, hypoproteinemia, severe anemia and an insulin demand, should have a complete abatement of symptoms, while C. L., controlled on diet alone, should show no improvement whatever other than the slow, gradual remission which

is often noted in these patients on a well regulated diabetes regimen. Neither patient showed roentgenologic evidence of regression of gastrointestinal atony, although in the case of E. S. the diarrhea disappeared rapidly.

Objectively, the so-called autonomic dysfunctions encountered in these subjects have remained unaffected. Gastrointestinal atony has remained

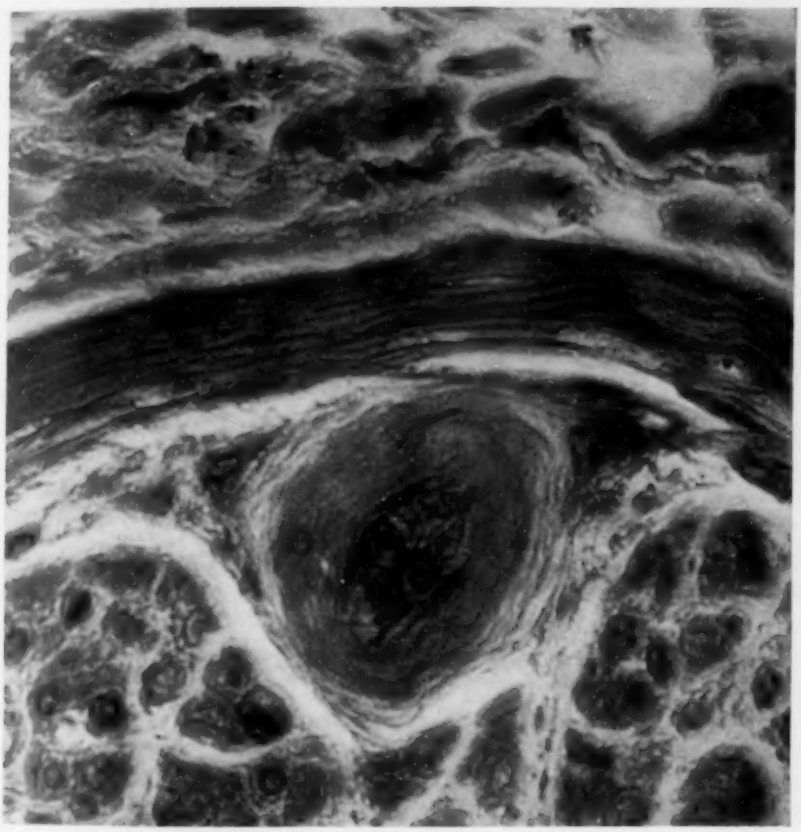

FIG. 3. Cross section of nerve bundle, showing an intrinsic arteriole. There are hyalinization and pronounced thickening of the media and swelling of the endothelial lining of the intima. (H. & E. stain. Photomicrograph, magnification × 450.)

unchanged, fixed pupils have remained so when present, and only one patient with impaired sweating showed a return to normal. Constipation, however, has been uniformly relieved. Both impotent patients recovered potency, but there is no sound evidence which would ascribe this to a specific effect of B_{12}.

It is of interest that the only subject failing to show an initial response to therapy was a "brittle" diabetic (J. C.), and only after a satisfactory regu-

lation of the blood sugar did he begin to show a response. The partial and temporary relapse in another patient we cannot explain.

The question arises: Is there any nonspecific analgesic or anodyne effect of vitamin B_{12}? Bean and associates [1] made clinical observations which indicated that this was not the case. We were not equipped to obtain graded responses to painful stimuli, but our clinical observations tend to support Bean's conclusions. B_{12} in dosages ranging from 15 y to 900 y once daily was administered for five to seven days to 10 patients with a variety of nerve root pain, including tabes dorsalis, cervical arthritis, alcoholic polyneuropathy and herpes zoster. In no instance was there a decrease in intensity of pain or frequency of lancinations. Other disturbed modalities associated with their illnesses were likewise unaffected. The following two cases are illustrative:

Case 1. M. L., a 52 year old white female, was seen two months after the onset of pain, subjective numbness and tingling of the fourth and fifth fingers of the left hand, and pain along the median aspect of the left forearm. There were hypesthesia of the hypothenar eminence and hyperesthesia of the volar surface of the fingers involved. The ultimate diagnosis was posterior nerve root irritation due to cervical arthritis. Nine hundred y of B_{12} were administered daily for three doses, and 20 y daily for seven more days. There were no changes in the above complaints.

Case 2. M. T., a 54 year old white female, complained of severe steady pain about the left aspect of the neck, shoulder and lateral surface of the upper arm. These areas were all hyperesthetic. After all diagnostic efforts had failed, B_{12} was exhibited in a dosage of 15 y daily for seven days, one month after the onset of symptoms. No change in either the pain or hyperesthesia occurred. Three weeks later the characteristic lesions of herpes zoster appeared.

Another possible, though unlikely, mechanism of action lies in the premise that B_{12} may cause dilatation of arterioles with improved blood supply to the nerve tissue. To test this hypothesis we studied several patients in a variety of ways, employing a Tycos dermatherm, as recommended by Rundles,[15] and the technic of Coller and Maddock.[4, 11] Patient J. C. was submitted to spinal anesthesia, and a moderate rise in the temperature of the lower legs occurred. Shooting pains were unabated. Skin temperature responses also were studied in this patient at constant room temperature extremes of 32° C. and 24° C. before and after the intravenous administration of 1,000 y of B_{12}. Responses remained the same. Two normal subjects with normal responses, and one subject with abnormal responses due to severe obliterative peripheral arteriosclerosis, were studied in the same fashion. Again no difference was noted before and after administration of B_{12}. Patient D. C. was studied several months after the amputation of the left leg, at a time when improvement in the right leg, foot and toes was sustained. Skin temperatures ranged from 29° C. to 23° C. at the two temperature extremes, substantiating the presence of obliterative vascular changes with a slight vasospastic component. The administration of 900 y of B_{12} intravenously did not alter these responses: Patient W. B. complained of calf pain on walking a measured distance, suggestive of inter-

mittent claudication. Exercise tolerance was greatly improved for three days following a spinal anesthetic, and a moderate sustained improvement was later obtained following the daily administration of Priscoline®. Nicotinic acid in a dosage sufficient to cause tingling of the nose and a slight facial flush was ineffective. Lancinating leg pains at rest had been permanently relieved by prior B_{12} therapy.

It appears that the improvement these patients have obtained is neither psychic nor on a vascular basis, but due to the action of vitamin B_{12} on the deranged intrinsic nerve metabolism, insofar as the latter is not the partial result of obliterative disease of the vasa nervorum. There is no evidence which would clarify the mode of action, whether it be intrinsic and direct, indirect, or mediated via new compound formation or catalytic to the utilization of other substances. Analogy to the results obtained by Horrigan and Vilter [8] in direct bone marrow maturation studies would suggest the likelihood of a direct, intrinsic mechanism.

Conclusions

1. In a series of 12 diabetic patients exhibiting the neurologic manifestations associated with the disease, and treated with crystalline vitamin B_{12} intramuscularly to the exclusion of therapy other than insulin and dietary control, we regard three as showing a complete neurologic remission, one as showing a complete remission after a partial relapse, three as being in almost complete remission, three as improved and two as questionably improved.

2. It is difficult to estimate how much nervous tissue damage is primary and how much is due to arteriosclerosis of the vasa nervorum and therefore presumably irreversible.

3. The response in such patients is variable and will be determined by the extent of vascular damage, as well as by the reversibility of injury to nerve cells. A satisfactory regulation of the diabetes with insulin and diet is not insurance against the development of neurologic derangements, but, contrariwise, improvement is not to be expected unless such effective regulation is instituted. It is doubtful that intrinsic spinal cord lesions can be reversed.

4. Exact dosage of B_{12} has not been established, and again the amount and frequency of administration will depend on the factors already mentioned. We recommend a flexible dosage of 15 y to 30 y daily the first seven to 14 days, followed by a maintenance dosage of 15 y to 30 y once or twice weekly. Frequency of administration appears to be more important than amount of individual doses used in achieving and maintaining a neurologic remission.

5. Massive doses of B_{12} do not appear to carry a cumulative effect, and should be reserved for the rare patient completely refractory to small amounts.

6. Vitamin B_{12} exerts a specific though unknown effect on the deranged nervous tissue metabolism in diabetes mellitus.

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OCULO-ORO-GENITAL SYNDROME: A DEFICIENCY DISEASE *

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I. INTRODUCTION

SINCE Gasper Casal first described "mal de rosa" some 200 years ago, many observers have noted that pellagra has varied considerably in its clinical manifestations. The variations of pellagra have received many designations: mild pellagra, pellagroid, pseudopellagra, pellagra sine pellagra, ariboflavinosis, hyporiboflavinosis, riboflavin deficiency disease, oro-genital syndrome and oculo-oro-genital syndrome.[1-11] Although these terms are confusing, they represent progress in the separation and classification of the various component deficiencies of the vitamin B complex.

Thirty-eight months of incarceration in several Japanese prisoner-of-war camps revealed that deficiency diseases run a gamut in a fairly regular order during protracted dietary restriction. The order, of course, depends upon the specific deficiency in the diet, and the time necessary for the body to become depleted of the specific vitamin.

Hypoproteinemic edema was common at the time of surrender of the American forces in Bataan and Corregidor during April and May of 1942. By July, 1942, scurvy was prevalent in the Cabanatuan Prison Camp, but it was quickly cured by the issue of a few limes to each prisoner. Scrotal dermatitis and stomatitis appeared in August, 1942, and affected the majority of prisoners. Painful feet [12-14] and optic atrophy [15] began in August and September of 1942. As the diet varied, remissions and recrudescences of the deficiency diseases followed.[16-19] The polyhypovitaminosis accompanying protracted dietary restriction caused much confusion to the medical officers who attempted to diagnose specific deficiency diseases.

Of all the various combinations of signs and symptoms which appeared, one syndrome stood out as being rather clear-cut, and has, for the want of a better term, been called the oculo-oro-genital syndrome.

II. DIET

The daily diet consisted of 200 to 400 gm. of a very poor grade of rice, 100 gm. of greens (weeds), and 10 gm. each of sugar, coconut oil, beans, sweet potato or corn, and meat. The diet averaged between 800 and 1,200 calories a day, of which protein and fat were about 50 calories each. Prisoners who were able to earn a pittance by hard labor on the "Farm" could supplement their diet with an occasional duck egg, banana, a few peanuts or a few beans.

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III. Scrotal Dermatitis

(The genital portion of the oculo-oro-genital syndrome)

When the first few cases of scrotal dermatitis appeared in August of 1942, the condition had the appearance of a trichophytosis and was thought to be caused by the poor sanitary conditions in the camp. Soap and water were advised, but they did not ease the condition or prevent the occurrence of many new cases each day. When glossitis and angular stomatitis appeared in the same individuals, the syndrome was recognized as a deficiency disease, probably closely associated to pellagra. In the following few weeks, more than 75 per cent of the 8,000 American prisoners developed some degree of scrotal dermatitis. One hundred moderately advanced cases were selected for study.

The scrotal dermatitis appeared rather insidiously and progressed through several phases: pruritus, erythema, exfoliation and ulceration. The erythema usually appeared first in the most dependent portions of the scrota and spared the raphe. In many prisoners the erythema extended anteriorly on to the ventral portion of the penis, and posteriorly around the anus. The erythema gradually became more intense and rather sharply demarcated, having the appearance of a first degree sunburn. Since shorts were one of the few articles of clothing universally retained by all of the prisoners, there was no reason to believe that the scrotal dermatitis in any case had resulted from exposure to the sun. All of the 100 cases of erythema ranged from moderate to severe. The scrota were hot to touch. Subjectively there were marked burning and itching, which were aggravated by any perspiration.

Exfoliation of small branny white scales appeared in 82 per cent of the selected cases from 10 to 30 days after the appearance of the erythema, and varied from mild to severe. In the severe cases the exfoliation involved the entire scrotum.

Superficial ulcers varying in size from a few millimeters to several centimeters appeared in 27 cases. The ulcers exuded a thin, serosanguineous fluid which continuously bathed and further irritated the scrotum and adjacent thighs. Some of the ulcers became secondarily infected. The prisoners became very apprehensive as to the possibility of sterility, impotence and even the loss of the scrotum. None of the selected cases progressed to those degrees, but several prisoners, not in the selected group, had a sloughing of one or both testicles.

IV. Accompanying Signs and Symptoms of the Oculo-Oro-Genital Syndrome

Within a few days of the appearance of the scrotal dermatitis, glossitis developed in all of the selected group and ranged from mild to severe. Its first manifestations were erythema and soreness of the tip of the tongue.

The papillae became swollen and denuded of epithelium. The denuded areas spread irregularly over the dorsum of the tongue, leaving patches of normal epithelium. The tongue became very sensitive to hot or highly seasoned food. Forty-one of the group developed typical geographic tongues. Sixteen cases progressed to raw beefy tongues, with deep ragged fissures on the dorsal surfaces. Twelve tongues developed ulcers varying from a few millimeters to 1.5 cm. in diameter.

Eighty of the selected cases developed angular stomatitis, ranging in degree from mild to severe.

Seventeen cases had striated mucous patches on the inner surfaces of the cheeks from 1 to 3 cm. in diameter.

Erythema of the pharynx and soft palate was seen in 59 cases. Crops of small sensitive ulcers appeared on the buccal membranes in 32 cases, especially over the hard palate.

Conjunctivitis, varying from mild to severe, developed in 93 per cent of the cases. Keratitis was present in some degree in 15 cases.

Diarrhea was present in 12 cases, but five were known to have amebic dysentery.

Thirty-seven cases developed some degree of burning of the feet one to three months following the scrotal dermatitis and glossitis. This was attributed to vitamin B_1 deficiency.

Twenty-eight cases developed some degree of amblyopia (optic atrophy) following the scrotal dermatitis and glossitis. This was attributed to vitamin A and B_1 deficiency.

Pigmentation of the exposed areas of the skin was a normal tanning, except for two cases who developed the typical pigmented dermatitis of pellagra.

Mental depression, apprehension, dizziness, muscular weakness, ease of fatigue and loss of weight were common complaints of all prisoners, so no special significance was attached to these symptoms, although they are all associated symptoms.

V. Treatment

There was very little medicine of any kind in camp, so treatment was practically nil. An excellent opportunity to determine the component of vitamin B complex to which the oculo-oro-genital syndrome would respond was lost.

VI. Adequate Diet

In December, 1942, and January, 1943, the prisoners each received two Red Cross parcels (11 pounds each) of American food and vitamins B_1 and C. It is estimated that the extra food and vitamins made the diet adequate for a period of about two months. During this time the signs and symptoms

of the oculo-oro-genital syndrome rapidly improved. The scrota became normal except for mild residual pigmentation.

VII. Return to Minimal Diet

When the diet at Cabanatuan Camp again became minimal, several months after the issue of the Red Cross parcels, the syndrome reappeared, but not to the epidemic proportions seen in August of 1942. It seems that the prisoners who had survived the first eight months of incarceration (2,400 had died from deficiency and tropical diseases during this period) had become somewhat adapted to the paucity of food and vitamins. Since many prisoners had lost from one-third to one-half of their body weight, their vitamin requirements were not so great as before.

VIII. Other Prisoner-of-War Camps

It is interesting to note that many prisoners in other tropical prisoner-of-war camps, where the diet had consisted mainly of rice but was inadequate in amount, developed the oculo-oro-genital syndrome in almost the identical interval of time. The syndrome had also been described in jails in India and Malay. However, in Korea and Manchuria, where the diet was also minimal but consisted mainly of corn and soy beans, the prisoners did not develop the syndrome.

IX. Absence of Many Signs and Symptoms Common to Pellagra and Hyporiboflavinosis

The following signs and symptoms which have been commonly associated with pellagra and hyporiboflavinosis were not commonly seen with the oculo-oro-genital syndrome:

1. Pigmented dermatitis of the exposed areas of the body. Although all of the selected prisoners were regularly exposed to the sun for several hours a day, only normal tanning of the skin occurred except for the two cases mentioned above.
2. Desquamation or other changes of the skin in the nasolabial folds and the ears.
3. Diarrhea, except for the seven cases noted above.
4. Nausea and vomiting.
5. Abdominal pain.
6. Nervous symptoms.
7. Mental changes: hallucinations, delirium or disorientation.
8. Paralysis.

X. Discussion

It seems unlikely that the oculo-oro-genital syndrome, which involved more than 75 per cent of 8,000 American prisoners and yet caused only 7

per cent diarrhea, 2 per cent pigmented dermatitis of the exposed skin, and less than 1 per cent mental changes, could be pellagra per se. However, all of the signs and symptoms seen in oculo-oro-genital syndrome have been frequently seen and described as being a part of the pellagra complex. It is probable that this deficiency is closely associated with pellagra and is possibly a deficiency of a specific component of the vitamin B complex.

XI. Conclusions

1. A deficiency disease comprised of an exfoliating dermatitis of the scrotum, stomatitis and conjunctivitis insidiously appeared in more than 75 per cent of 8,000 American prisoners-of-war after six months of an inadequate rice diet.

2. The syndrome was quickly and markedly improved by two months of adequate diet.

3. On return to inadequate rice diet, the syndrome was far less prevalent, indicating some adaptation of the body to lowered caloric and vitamin intake.

4. The vitamin requirements of the body appeared to be less after a loss of considerable body weight.

5. The syndrome did not develop on a minimal diet composed of corn and soy beans.

6. The syndrome is thought to be closely associated with pellagra, but not pellagra per se.

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REVITALIZATION OF TISSUE AND NUTRITION IN OLDER INDIVIDUALS *

By William B. Kountz, M.D., *St. Louis, Missouri*

It has long been considered that changes occurring in the body due to aging are irreversible. If such were a clearly established fact, the field of geriatric medicine would be greatly limited.

Since the retrogressive changes in the female reproductive tract fall into a special category and are the changes brought about by exhaustion of ovarian function, these tissues in old individuals from 60 to 95 years of age and long after the menopause were chosen for observation as to revitalization of older tissue and to test the theory of whether changes in older tissue are reversible or not.

In order to study the changes in the reproductive tract we began the observations by a complete medical check up of a group of older women from 50 to 95 years of age. Careful studies were made of the cardiovascular system, pelvis, and genito-urinary system, with special attention to evidence of pathology, in general, and particularly of the breast and genital tract. As nearly as possible a careful endocrine evaluation was made, and evidence of any nutritional defects was noted. Individuals with advanced acute or degenerative disease, aside from arteriosclerosis, were considered to be poor risks for prolonged study and were not selected. All individuals were inmates of the St. Louis City Infirmary and Infirmary Hospital and, consequently, some showed defects such as senile mental changes, particularly mixed psychoses, arteriosclerosis and other common changes of the degenerative phase of life. A total of 60 individuals has been studied for various periods, some as long as six years.

Those individuals selected were given 1 mg. of estradiol benzoate 2 times per week as a basic medication, and progesterone or testosterone which we found could be used interchangeably, 5 mg. daily for different lengths of time. The majority of them, however, received this latter medication after bleeding had been induced, 20 days after the last menstrual period. All medication was given intramuscularly.

In one set of observations 30 individuals were chosen for a study and were given careful medical and gynecological check up and were isolated in a large ward. Fifteen of these were given the regular dose of estrogen and androgen, and 15 were given oil in the same type of ampule. The purpose of the isolation of this group of patients was to establish the influence of the hormones on the psychological behavior of the patients. It was necessary

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at the time of the physical examination to give these individuals initial psychological tests and this was done by a psychologist who was to follow them throughout the period of study. The nurse in charge did not know which patients were receiving the medication or which the plain oil, and, what is more important, neither did the psychologist who was examining the group know which was receiving the medication until after she had completed her studies.

In all the individuals studied and in the special group of 30 the controls as well as the individuals who received medication were examined by vaginal smears. These were stained by the iodine vapor technic of Mack.[1] We found, as have others,[2] that in the senile resting states of older women relatively few epithelial cells were obtained by the vaginal smear, and the cells demonstrated a very poor ability to take the iodine. After the injections were begun there was an increase of cells in the vaginal smears and also in the amount of iodine taken up by this tissue. By following the vaginal smears taken at regular intervals of three months it was possible to estimate the degree of stimulation during the period of study. Vaginal smears were taken at regular three month periods and have shown as much as 85 per cent stimulation.[3]

A study of the endometrium of the uterus by biopsy was made initially before therapy and during the course of the observation. The typical biopsy obtained from the resting senile endometrium showed that the cells in the stroma were compact and seemed to be compressed together. Careful microscopic scrutiny revealed that they were relatively small in size compared to those of a premenopausal uterus. The glands were shown as relatively small areas compressed within the stroma. Their cells were small and the nuclei were crowded at the base with a small central canal which was difficult to recognize in some sections. It is generally characteristic that no blood vessels were distinguishable in this type of tissue.

After stimulation of the tissue one found a decided change. These changes consisted of a modification of the stroma which was found to be less compact and more edematous. The gland cells in the endometrium had much more cytoplasm at the base than they did before. The nuclei were found toward the lumen of the ducts. The gland cells had increased in both length and diameter and the tissue resembled more that of premenopausal individuals. The lumina of the glands were large and with proper staining revealed a mucoid material. Many small blood vessels were noted in tissue taken at this time. These observations, we believe, establish the fact that the genital tissue of the body aside from the ovary can be reactivated and caused to regain a more normal appearance as well as an increase in activity.

When our studies were first begun we were anxious to know if the tissues could be stimulated without development of disease since stimulation in animals indicated that such might be the case.[4] We are able to say at this time after following a group of patients for a period of six years that

during our observations there has been no evidence of disease in any form. This includes evidence of malignancy in any tissues.

After having made these preliminary observations which indicated that there must be an increase in the blood supply to the uterus, we were ex-

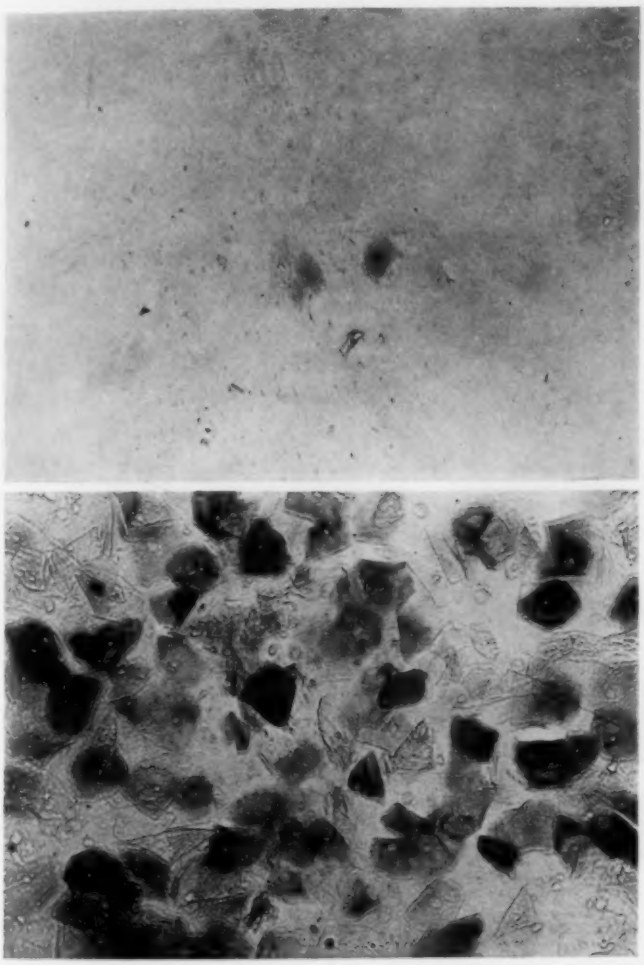

FIG. 1 (*above*). A typical photomicrograph (× 250) of a vaginal smear from a senile individual. One notes relatively few epithelial cells which stain poorly with iodine, many of which are disintegrated.

FIG. 2 (*below*). A vaginal smear (× 250) after a period of injection with estrogen and progesterone. One notes the large increase in the number of cells and the deep staining quality of some.

ceedingly anxious to know what did happen to the blood vessels which, in old women, are found to be very arteriosclerotic. Would these arteries be incapable of carrying adequate amounts of blood, and hence we would

expect to find infarcts and scars in the uterine wall, or would these sclerotic arteries respond to the increased demand for blood? In order to make this observation it was necessary that we study the body of the uterus and its blood supply. For this it was necessary that we rely on postmortem ex-

FIG. 3 (*above*). Biopsy of the endometrium (× 250) of the uterus of an elderly female before stimulation. One notes that the cells are compact, that the glands are small and the nuclei of the cells are near the base, with relatively little cytoplasm in the cells.

FIG. 4 (*below*). Tissue taken at time of menstruation (× 250). One notes considerable hemorrhage, and that the glands form a great part of the picture. These have increased in size. The cytoplasm of the gland cells is away from the duct. The appearance is typical of that of tissue taken from women at an earlier age.

aminations. Since we could not measure the change that occurred in any one individual it was necessary that we have controls of about the same age for the study. We chose older women, therefore, of about the same age

and with a similar gynecological history and examined the uteri and compared them with those of the individuals in our study whom we were following to the postmortem table. Thus, we would compare the uterus of an individual who had had no children with a similar control. Likewise, we were careful not to compare the vessels of the uterus of an individual who had congestive heart failure before death with one who did not, because of the influence of congestion on the tissue. The controls consisted of older women who had not received medication but who came to the postmortem table under similar circumstances of our treated group.

A comparison of blood vessels taken at autopsy from the uteri of the elderly individuals in the control group showed an advanced arteriosclerosis.[5] Many of the large arteries were sclerotic and calcified and those in the muscle of the uterine wall showed marked hyalinization of the walls. The lumina of the vessels in most instances were very small and relatively little blood could have gone through them. In contrast, one could note in the blood vessels of the uteri of individuals who had received the injections that the lumina are relatively large in diameter even though some did have deposits of calcium in the media. Another point which we consider extremely important is the significant loss of the hyalin material in the vessel walls and the reappearance of normal muscle tissue in place of the dense hyalin always seen in the artery walls of the senile uterus. This is a definite change and in many cases observed by Masters and ourselves over a period of several years a replacement of the hyalin material in the vessels by normal muscle cells was noted. These observations are being reported by Masters in detail in a separate communication.[5] In none of the uteri studied have we found evidence of infarction or scarring which would lead us to believe that the increase of function had caused a reduction in blood supply to any area. We have interpreted these observations as a lessening of the arteriosclerotic process which suggests that one of the causes of arteriosclerosis may be a reduction of physiological activity of the organ. If this may be interpreted parabolically it could apply to other tissue in the body and as well to the entire organism since it is known that there is a general lessening of all tissue function with age.[6]

In the course of the therapy we noted, in many instances, changes such as painful breasts, so often seen in younger women, and on biopsy of the tissue before and after stimulation, we found changes in size and character of the cells of the ducts and glands.[7] This led us to consider what other tissues of the body might be involved in this process of stimulation. Biopsy of the skin, muscle, and mucous membrane of the nose and throat were the only other ones that could be readily undertaken in our setup. Response of the skin to the treatment was slow, but over a period of years we found that papillae had become deeper and an increase in vascularity could be demonstrated.

Biopsy of the mucous membrane of the nose was obtained before the medication was administered and showed, according to otolaryngologists,[8] a typical senile mucous membrane, which consisted of a piling up of the cells of the membrane resembling pseudo-squamous arrangement, loss of cilia and a decrease in the blood supply.

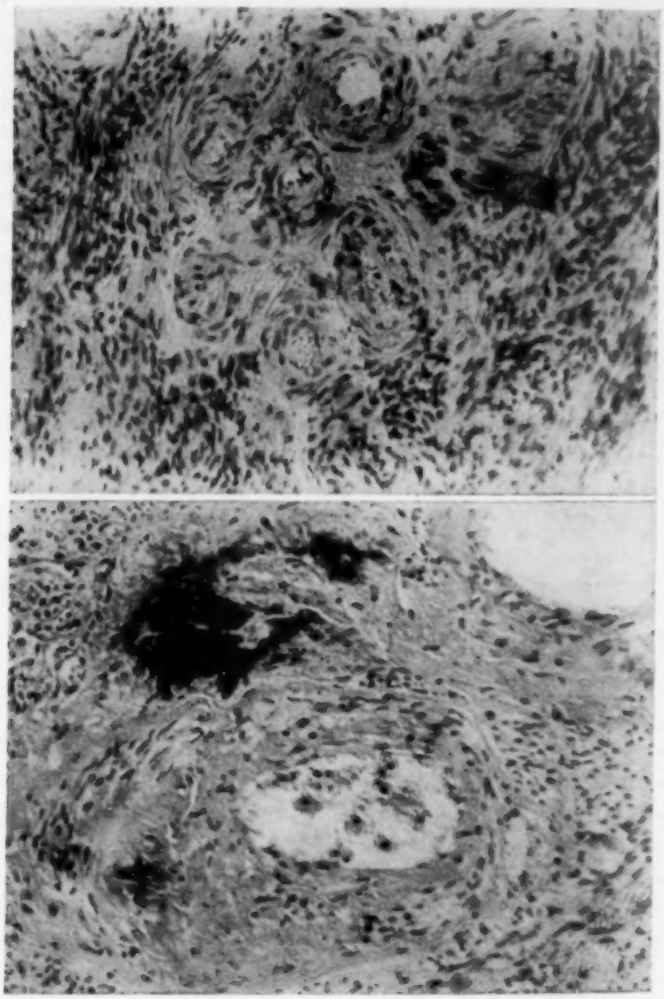

FIG. 5 (*above*). Photomicrograph of a section of a uterus of a 68 year old female. One notes a group of arteries and the relatively small size of their lumen. The dark areas in the walls contain calcium.

FIG. 6 (*below*). Photomicrograph of a structure through the wall of a uterus of an 82 year old female, who had menstruated monthly, for three years. She had received treatment for 38 months. One notes the large size of blood vessels, and a reduction in density of the hyalin material when compared to figure 5. The calcium in the vessel wall may be readily identified.

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The changes occurring after one and one-half years of therapy consisted of a return to a more normal mucous membrane. The findings consisted of a thinning of the mucous membrane, the redevelopment of cilia, and evidence of increased vascularity. Such a picture when shown to anatomists suggested a normal mucous membrane.

Examination of the deep structures of the tissue of the nose revealed a flat type of epithelium surrounding plugs of mucus, before stimulation, with glands which were small and diminished in diameter with little evidence of vascularity in the surrounding tissue. After a period of a year following the start of the injections a more normal state was noted in the glands of

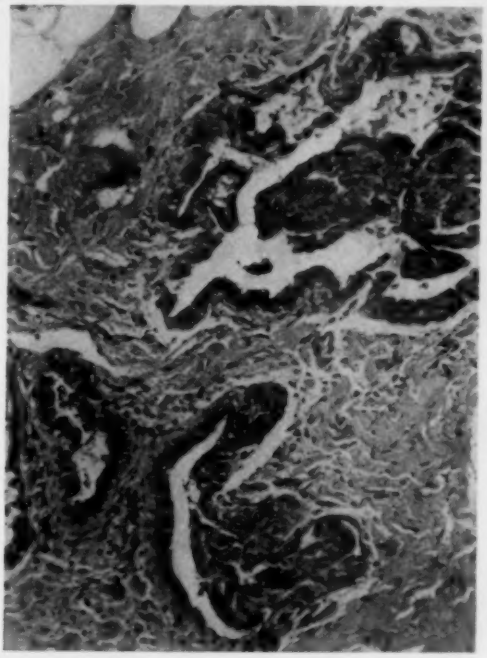
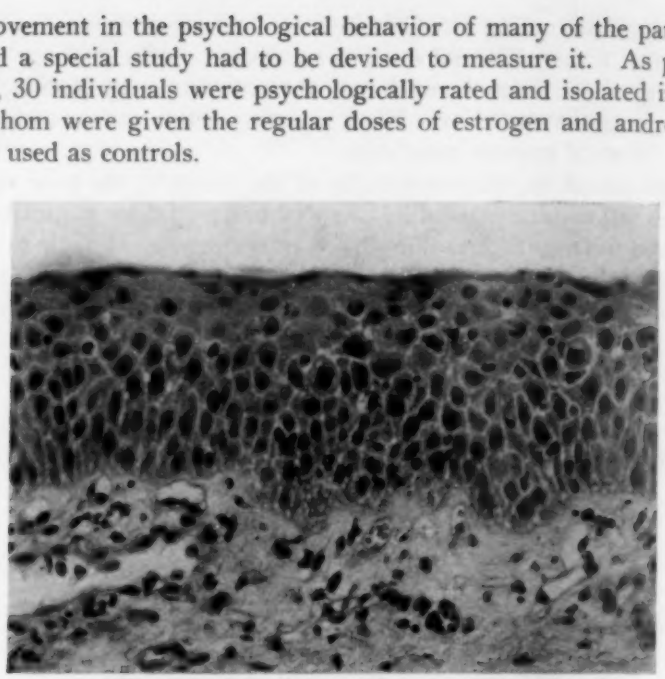


FIG. 7. Biopsy of breast tissue taken after administration of estrogen from an elderly female. One notes quite a normal appearance of the tissue after stimulation.

these tissues, and a more typical cuboidal type of cell and many functioning glands could be seen. Many of the cells could be demonstrated as producing mucus in contrast to those seen in the resting state in the same individuals. According to otolaryngologists this represented quite a normal appearance for this tissue.

We can conclude, therefore, that the sex hormones do not limit their activity to tissue associated with the genital tract, but appear to have a stimulating effect on all epithelial tissue that we have studied. At autopsy we have not been able to note any definite changes in any internal organs, aside from the uterus, with the possible exception of the kidney.

Improvement in the psychological behavior of many of the patients was noted and a special study had to be devised to measure it. As previously indicated, 30 individuals were psychologically rated and isolated in a ward, half of whom were given the regular doses of estrogen and androgen, and half were used as controls.



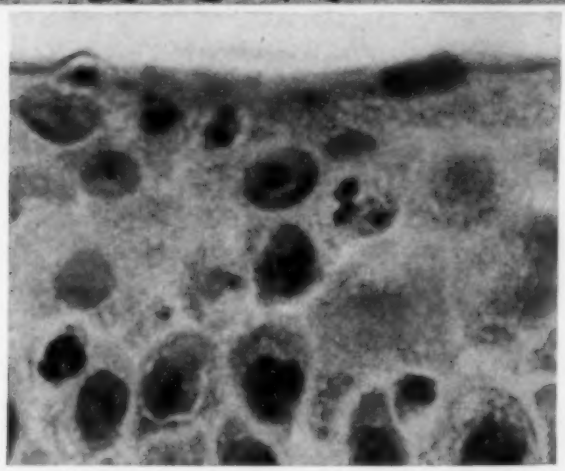
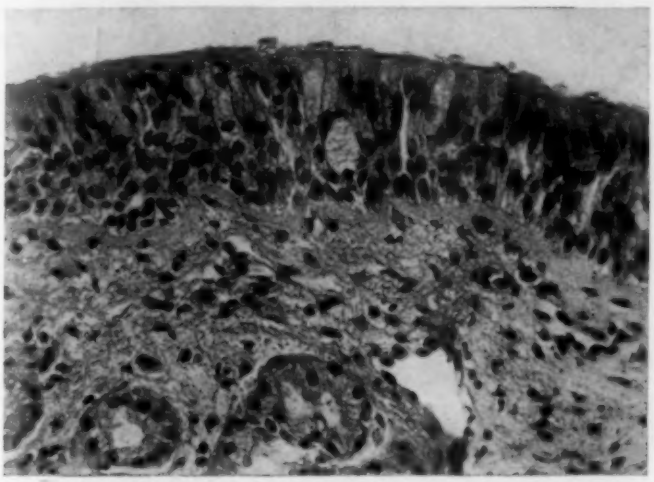


FIG. 8 (*above*). Photomicrograph (× 250) of the nasal mucous membrane of a 75 year old female before the study was begun. One notes the piling up of epithelium resembling that of a pseudo squamous nature.

FIG. 9 (*below*). Photomicrograph (× 1,200) showing the edge of the nasal mucous membrane. One notes particularly the absence of cilia in the unstimulated elderly female. There appear, however, to be a number of mytotic figures.

A full report of the psychological changes found in the treated subjects is now in press,[9] but a brief summary can be reported here. Performance on intelligence tests did not show uniform improvement, but there was a

distinct trend for the better, especially when ability to think and willingness to expend effort were required for successful performance. Memory functioning showed clear and unequivocal improvement, even when the material to be retained had little meaning for the subjects. Often when there was no improvement in intellectual functioning there was less decrement in per-



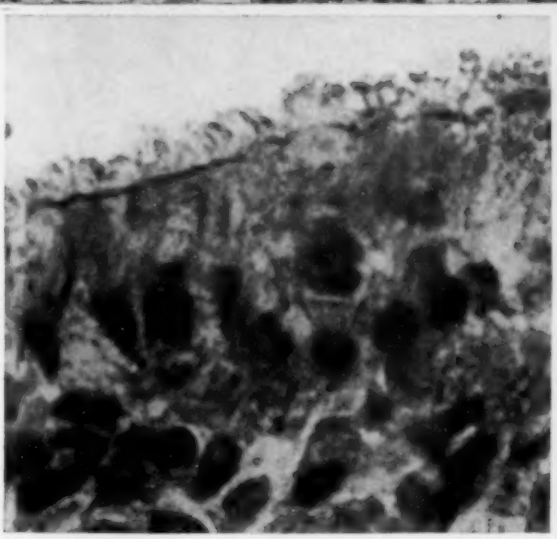


FIG. 10 (*above*). Photomicrograph (× 250) of the mucous membrane of the nose from the same patient as in figure 8. One notes an increase in mucous glands in the epithelium, the presence of cilia, and likewise a thinning of epithelial tissue and a more nearly normal appearance of the tissue after stimulation.

FIG. 11 (*below*). Photomicrograph (× 1,200) showing the presence of cilia on the mucous membrane, same as figure 9, after stimulation. Likewise one notes an absence of the mytotic figures seen previously.

formance level than appeared in the control group as a result of the passage of time. In addition, the patients demonstrated a decrease in rigidity of habit patterns, a modification which is very crucial for adaptive behavior in

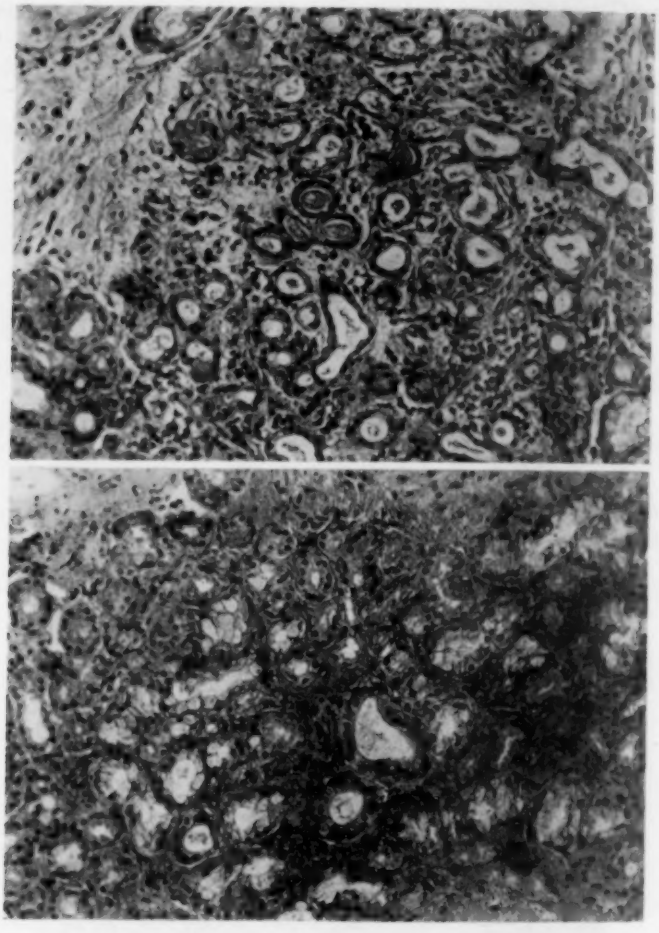


FIG. 12 (*above*). Photomicrograph (× 250) of a senile mucous membrane of the nose, showing the deeper glandular structure. One notes particularly the small size of the glands and also the cells. Many of the ducts appear to have small bits of material within them.

FIG. 13 (*below*). Photomicrograph (× 250) taken from the deep layers of the mucous membrane of the nose, showing the ducts. The gland cells appear to be filled with a mucoid material. The cells and ducts in general are increased in size. This photomicrograph showed, according to the otolaryngologists, a marked increase in function of these tissues after stimulation.

the aged. It was felt by the examining psychologist that many of these changes were related to a general increase in motivation to succeed and to perform maximally.

We have been interested in the mechanism by which these changes occur and in order to determine this we have made a large group of studies, some of which include a loading test for glucose, basal metabolic rate, as well as the nitrogen balance. We have attempted to determine the glycogen content of the skin and muscles and vaginal secretions.

The value of the glycogen content of tissues has been difficult to establish. Some of the methods used indicated an increase in its content in both skin and muscle after the use of the estrogens and androgens while others did not

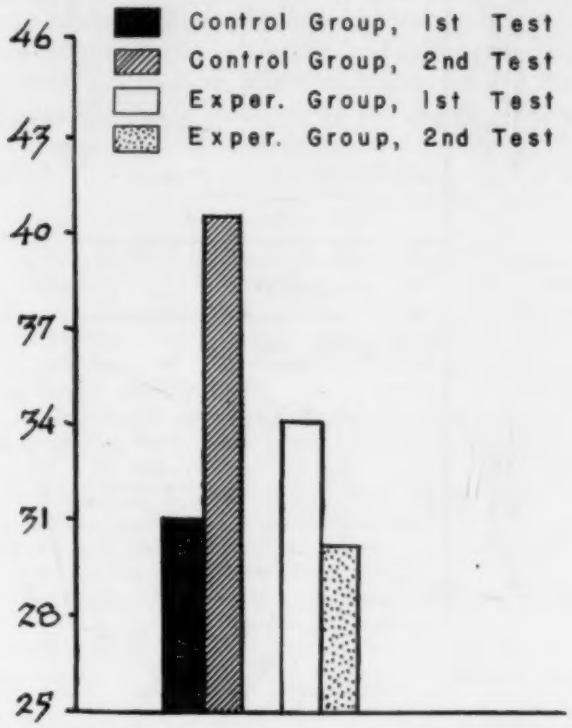


FIG. 14. Chart of the amount of deterioration as measured by the deterioration index of the Wechsler-Bellevue intelligence scale. Between the first and second examinations the per cent of deterioration has increased in the control group, and decreased in the experimental group.

verify this. However, one constant finding has been a definite increase in the protein sparing action on the body.[10]

The estrogens when given alone under circumstances of a low protein intake did have some protein sparing action which could not be recognized when the protein in the diet was increased above 1 gm. per kilogram of body weight per day. The androgens, on the other hand, increased the protein sparing action both with low protein diets, and high protein intakes. In all the studies the total calories were kept constant in the individuals and the patients were ambulatory.

Since there was improvement in the general nutritional condition in many of these patients and in some a remarkable increase in physical strength and improvement in aspects of the mental state, we feel that these so-called

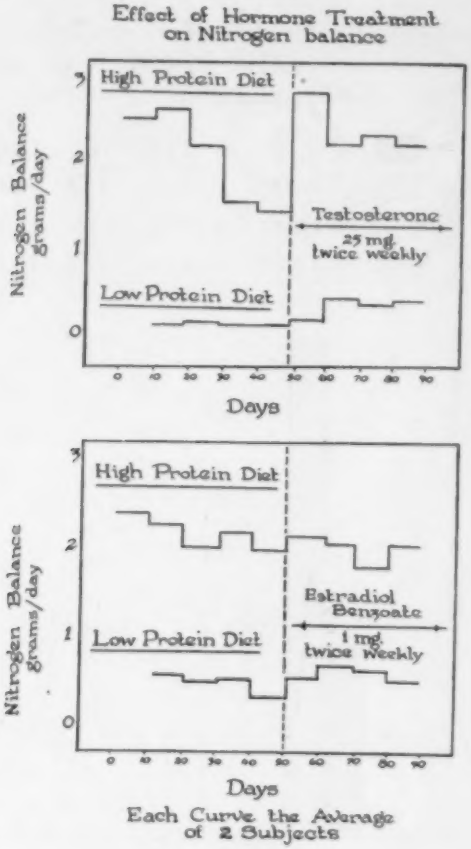


FIG. 15. Chart showing the effect of estrogens and androgens on nitrogen balance in both high protein diet, 1.5 gram per kilogram of body weight per day, and low protein diet, .5 gram per kilogram of body weight per day. On the low protein diet a definite increase in the nitrogen retention was noted with 25 mg. of testosterone twice weekly. When estradiol benzoate, 1 mg. two times a week, was given, some nitrogen retention was noted on the low protein diet, but none was noted when the protein intake was increased above 1 gram per kilogram of body weight per day. The administration of androgens with the high protein diet did have a protein sparing effect, although less than when the individuals were on a low protein intake.

sex hormones act generally on the body as nutritional factors which suggests that they are one of the many links in the chain of the control of degeneration associated with age.

Summary

We may conclude from our observations that certain tissues associated with age may be revitalized by use of estrogen and androgen to the point where it can be restored to function and appearance of an earlier period of life. This revitalization process is not associated with disease if the doses are held within physiological bounds; that returning tissue to improved function may not be inhibited by arteriosclerosis but the arteriosclerotic factor seems to be lessened which suggests that certain forms of arterial degeneration may be the result of physiological inactivity.

The primary action of the estrogenic and androgenic substances, according to our studies, is a direct effect upon nutrition of the body. The result of the improvement is a lessening of the degenerative state in some categories and in many individuals some retardation of both the mental and physical decline.

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COCCIDIOIDAL MENINGITIS: REPORT OF FOUR CASES WITH NECROPSY FINDINGS IN THREE CASES *

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SINCE Wernicke's original description in 1892 of the disease coccidioidomycosis,[1a, 1b] knowledge of its natural history has been greatly expanded. A complete review of this information is beyond the scope of this report; however, certain important facts may be summarized as follows:

It was not until 1937 that Gifford and Dixon [2, 3, 4] established the relationship of the benign disease known as "valley fever" or "desert rheumatism" to the serious infection known as coccidioidal granuloma. Both were caused by the organism *Coccidioides immitis.* The endemic areas of infection in the United States [5] were well recognized prior to 1941.

The signs and symptoms of primary coccidioidal infection are variable. Sixty per cent of the cases are asymptomatic. Forty per cent develop symptoms resembling a severe cold or mild pneumonia within a period of one to three weeks after exposure.[13] The primary infection may be complicated by erythema nodosum and polyarthritis in from 4 per cent to 25 per cent of the cases. This is associated with a hypersensitive state which is thought to confer a lasting immunity to reinfection and to the progressive form of the disease.[6, 8, 14, 15]

The disseminated form of the disease occurs in approximately .05 per cent to .2 per cent of the cases of the primary infection.[6, 7, 8, 9, 10] The mortality rate of the disseminated form of the disease is approximately 50 per cent.[11] Twenty-five per cent of those dying in this group show pathologic evidence of meningitis.[1, 12] When the meninges are involved the disease is uniformly fatal.

On the basis of extensive clinical material, Smith [13] concluded that dissemination usually occurs early in the course of the infection, soon after the disease is acquired, and that dissemination never occurs in patients with cavitary pulmonary disease due to coccidioides.

Forbus,[1] however, maintained that late dissemination of the disease was not infrequent. He found what he considered to be the focus of dissemination in the lungs. Histologically, the focus was the oldest lesion present.

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In these cases, the clinical symptoms of meningitis had appeared many months after the pulmonary disease was considered inactive.

Several pathologic types of coccidioidal meningitis have been described. Abbott and Cutler [16] classified their cases into two groups, acute and chronic. There were seven instances of acute meningitis associated with systemic infection. The longest duration of meningeal symptoms was three months. The second group classified as chronic meningitis showed pathologic changes limited to the primary meningitic disease. The longest duration of meningeal symptoms was one year. All of the chronic cases had moderate internal hydrocephalus.

Forbus [1] described two histopathologic types of coccidioidal meningitis. The granulomatous type occurred most frequently in his cases. This was a firm, plastic type of meningeal inflammation which was highly organized and encased the brain substance, particularly the brain stem. The exudative type of the disease showed pronounced exudation of fluid, with wandering cells and polymorphonuclear leukocytes and only minimal granulomatous tissue reaction.

In the disseminated form of the disease, numerous therapeutic agents have been employed with little success. These include heavy metal (copper, arsenic, gold, bismuth [7, 9, 20, 18, 19]), dyes (acriflavin, quinacrine, gentian violet [20, 21]) and other drugs (emetine, iodides [22, 23]). Other agents, such as vaccines, convalescent blood and roentgen-ray therapy have been used.[7, 9, 14, 24, 25, 26] The more recent chemotherapeutic agents (sulfonamides [5, 20, 27, 28, 29]) and antibiotics (penicillin, streptomycin and aureomycin [30, 31, 32, 33, 34]) have also proved ineffective.

The following four cases of coccidioidal meningitis are presented to emphasize: (1) the chronicity of this form of meningitis; (2) the resistance of coccidioidal meningitis to treatment; (3) the importance of considering coccidioidomycosis in the differential diagnosis of chronic meningitis, and (4) the effect of the fungicide Actidione.

Case Reports

Case 1. A 36 year old white male veteran of World War II was admitted to the hospital on February 17, 1947. He complained of severe pain, fever and cough of 10 days' duration. In November, 1943, while serving in the infantry in the region of Flagstaff, Arizona, he noted a pleuritic pain in the left chest. Within a few weeks he developed fever and was admitted to the Tourney General Hospital (Army) in California. Low-grade fever, persistent cough which had become productive, weakness and weight loss were present. There was roentgen-ray evidence of cavitation in the left lower lung field. The skin test for coccidioidomycosis was positive. After the cough and fever subsided, he was discharged from the Army in May, 1944. The veteran's records show that a roentgenogram of the chest taken in May, 1946, was interpreted as revealing no evidence of cavitation or residuum of the process previously seen.

Following discharge from the service, he noted recurrent chest pain and complained of nervousness and headache. He had persistent anorexia with occasional

vomiting and lost 30 pounds in weight during this interval. Three weeks prior to admission the frontal and occipital headaches became more severe. Ten days before admission he developed a sore throat and fever, followed by right chest pain and a productive cough. There was no hemoptysis. He had nausea and vomited frequently for three days.

General Physical Examination: The patient appeared both acutely and chronically ill, agitated and somewhat confused. Temperature was 102.6° F.; pulse, 105; respirations, 22; blood pressure, 120 mm. Hg systolic and 70 mm. diastolic. There were moist inspiratory râles and signs of consolidation over the right lung base. No abdominal viscera or masses were palpated. The anterior and posterior cervical lymph nodes were slightly enlarged. The mucous membranes and nail beds appeared pale and moderately cyanotic. On neurologic examination, only an equivocal left Babinski's sign and slight anisocoria were demonstrated. There were moderate nuchal rigidity and an equivocal Kernig's sign.

Laboratory Examination: The admission hemogram revealed 4,260,000 red blood cells; hemoglobin, 12.5 gm.; white blood cells, 23,600, with 98 per cent neutrophils and 2 per cent lymphocytes. Urinalysis showed the presence of 1 plus albumin, many white cells and occasional red cells. The blood Wassermann and Kahn tests were negative. Spinal fluid examination at the time of admission revealed an initial pressure of 380 mm.; 566 white cells, of which 85 per cent were neutrophils and 15 per cent lymphocytes; protein, 123 mg. per cent; sugar, 13 mg. per cent; chlorides, 688 mg. per cent; cultural studies, negative.

Repeated cultures of sputum, gastric washings and spinal fluid were negative for fungi. Guinea pig and mouse inoculations of the spinal fluid and sputum were negative. Subsequent blood counts and urinalyses were normal. The sedimentation rate was 35 mm. per hour and remained elevated throughout the hospital course. The kidney and liver function tests were normal.

Roentgen-ray examination of the chest on admission disclosed a pneumonic process in the right lower lobe of the lung; however, subsequent roentgenograms of the chest following penicillin therapy were normal except for a moderate degree of pulmonary emphysema. Roentgen-ray examinations of the skull, paranasal sinuses and the long bones of the skeleton were within normal limits.

Serologic tests on March 15 for coccidioidal infection revealed a complement fixation of 4 plus in 1:16 dilution and 1 plus in 1:32 dilution, and negative precipitin tests. These tests were interpreted as indicating a moderately severe infection, having occurred sufficiently in the past for precipitins to have been lost.* Skin tests for tuberculosis (P.P.D.), first and second strength, were negative in 72 hours. Skin tests for coccidioidomycosis, using coccidioidin 1:100 dilution, was positive in 72 hours (erythematous indurated area, 1 cm. in diameter).

Penicillin therapy was begun a few hours after admission and was continued for approximately 60 days. Within 18 hours of admission the patient was afebrile, with marked improvement as manifested by a decrease in cough and reduction in the quantity of sputum. Lumbar punctures afforded complete relief from headaches.

On March 19, signs of sixth nerve paresis on the left and ptosis of the left eyelid were observed, associated with severe frontal headaches, nausea and vomiting. On April 4 patient had two convulsive seizures, beginning on the left side of the body. Ventriculographic studies on April 8 revealed symmetrical dilatation of the ventricular system. By April 14 he exhibited a coarse tremor of the hands, generalized hyperreflexia, cogwheel rigidity with moderate spasticity of the muscles of the extremities, and incontinence of urine and feces. The ptosis of the left eyelid and nuchal rigidity

*The serologic tests for coccidioidal infection presented in this paper were obtained through the courtesy of Dr. C. E. Smith, Professor of Public Health and Preventive Medicine, Stanford Medical School, San Francisco, California.

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persisted. He received a total of 31 gm. of streptomycin intramuscularly during a period of approximately one month. Potassium iodide, saturated solution, 0.5 c.c., was given three times daily. On May 9 he had a convulsion which lasted approximately one hour. Anorexia and occasional vomiting had accounted for a weight loss totaling 45 pounds by August, 1947.

Actidione therapy was begun on July 10, 1947. Patient received intravenously each day 30 mg. of Actidione diluted in 1,000 c.c. of 5 per cent glucose in distilled water. A total of 300 mg. of Actidione was given. Spinal fluid examination on July 10 revealed a pressure of 300 mm.; 696 white cells with 78 per cent neutrophils and 22 per cent lymphocytes; protein, 229 mg. per cent; sugar, 25 mg. per cent, and a sterile culture. During Actidione treatment, disorientation became a prominent feature; however, complete remission of the sixth nerve paresis and the left lidlag occurred. Incoördination of the extremities, spasticity and generalized hyperreflexia persisted. Serologic tests on July 17 revealed the following: Serum complement fixation tests for coccidioidal infection revealed 4 plus fixation in 1:32 dilution and 1 plus in 1:64 dilution. Complement fixation on spinal fluid: 4 plus in 1:32 dilution and 1 plus in 1:64 dilution. Precipitin tests on both spinal fluid and serum were negative. The increase in titer in the serum and spinal fluid was interpreted as indicating further progression of the disseminated coccidioidal infection and a grave prognosis.

In the latter part of August clinical improvement began. In the following eight months of hospitalization patient gained slowly in strength and showed improvement in coördination. By February 11, 1948, he had regained the weight lost during his illness. He became ambulatory and mentally clear, and regained bowel and bladder control. The positive findings were limited to slight tenderness in the right upper quadrant of the abdomen, slight spasticity of the extremities and moderate instability of gait, hypermetria of the right finger-to-nose test, with generalized hyperreflexia of the deep tendon reflexes. Spinal fluid examination on February 2, 1948, revealed a pressure of 180 mm.; 56 white blood cells, of which 54 per cent were neutrophils and 46 per cent lymphocytes; protein, 212 mg. per cent; sugar, 23 mg. per cent, and negative smear and culture of the spinal fluid. Serum complement fixation for coccidioides had fallen to 4 plus in 1:16 dilution and 1 plus in 1:32 dilution. He was discharged from the hospital on March 17, 1948. Following discharge he continued to be ambulatory; however, he failed to regain his usual weight, as noted on a follow-up examination on June 6, 1949, but was alive on February 5, 1950.

Summary: This patient had developed a cavitary pulmonary lesion while in Flagstaff, Arizona, which was followed three years later by coccidioidal meningitis. Serologic studies for coccidioidal infection were compatible with a disseminated form of the disease. For many months he was critically ill and failed to respond to streptomycin, penicillin and potassium iodide therapy. He was given Actidione intravenously, following which he showed a delayed but quite remarkable clinical response and was alive three years after he was first found to have meningitis.

Case 2. A 27 year old Negro male was admitted to the McKinney Veterans Hospital on June 17, 1947. His chief complaints were "dizzy spells" and headaches of four years' duration. While in the Army, stationed at Camp Roberts, California, in February, 1943, he developed pleuritic pain in the right chest. One week later he complained of severe frontal headaches and stiff neck, for which he was treated in the hospital in March, 1943. At that time the physical examination was said to disclose no abnormalities other than moderate nuchal rigidity. Blood Wassermann and

Kahn tests were negative. The initial spinal fluid examination showed 2,750 white cells, with 84 per cent neutrophils; sugar of 56 mg. per cent; "normal" chlorides; 4 plus globulin; protein of 100 mg. per cent, and a colloidal gold curve of 0002211000. Smears and cultures of the spinal fluid were negative. Guinea pig inoculations of the sputum, gastric washings and spinal fluid revealed no fungi or tubercle bacilli. Roentgen-ray examination of the chest in March, 1943, showed a small area of infiltration in the right sixth interspace, which resolved very slowly on subsequent examinations. Roentgenograms of the skull and encephalograms were reported to show obliteration of the subarachnoid spaces overlying the convex surface of the cerebral hemispheres.

He was placed on sulfadiazine therapy. The nuchal rigidity improved rapidly. The headaches, vertigo and nausea persisted but were less severe. The lung lesion and symptoms improved slowly on symptomatic therapy. He was discharged from the Army in February, 1944, with a diagnosis of "Residuals of chronic meningitis, cause undetermined." He returned home but was unable to work because of slight headaches and infrequent dizzy spells.

In November, 1946, he noted loss of appetite. Vomiting without nausea occurred one to two times per day. He lost approximately 25 pounds in weight in three years. Four months prior to admission to this hospital he had a recurrence of throbbing frontal headaches, severe enough to confine him to bed. The past history was otherwise not contributory.

On physical examination he appeared to be chronically ill, coöperative, but disoriented. His speech was slow and thick, and there was partial loss of memory for past events. His temperature was 99.6° F.; pulse, 85; respirations, 20; blood pressure, 105 mm. Hg systolic and 70 mm. diastolic. There were nystagmoid movements on right lateral gaze. The pupils were dilated and equal and reacted sluggishly to light and accommodation. The funduscopic examination was within normal limits, but the visual fields were moderately constricted bilaterally. The chest was normal and both lung fields were clear. Abdominal examination revealed no abnormalities. Patient showed generalized tremulousness and muscle weakness, but no fibrillary twitching, paralysis or atrophy. The superficial and deep reflexes were equal and active. The Babinski's sign was negative bilaterally. The cranial nerves were intact. There were mild nuchal rigidity and a questionable Kernig's sign.

Laboratory Examination: The hemogram on admission revealed 4,630,000 red blood cells; white blood cells, 4,500, with 43 per cent neutrophils, 48 per cent lymphocytes, 6 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. The hemoglobin was 12.1 gm. Urinalysis was normal. Blood Kahn and Wassermann tests were negative. The sedimentation rate was 2 mm. per hour on admission and remained normal on repeated examinations. Spinal fluid examination revealed a pressure of 140 mm.; 160 white cells with 68 per cent neutrophils and 32 per cent lymphocytes; protein, 382 mg. per cent; sugar, 5 mg. per cent, and no growth on cultural studies. Mouse and guinea pig inoculations with the spinal fluid disclosed no organisms. Repeated blood counts and urinalyses were all within normal limits. Roentgen-ray examination of the chest on June 19, 1947, was within normal limits. Stereoscopic roentgen-ray examination of the skull revealed complete absence of the posterior clinoid processes and marked enlargement of the sella turcica. The petrous ridges were blunted and eroded. A calcified pineal gland was not displaced. Complete roentgen-ray survey of the long bones showed no abnormalities. Serologic tests on July 7 for coccidioidal infection showed the following: serum complement fixation, 4 plus in dilution 1:16 and 2 plus in 1:32 dilution; complement fixation from spinal fluid, 4 plus in 1:16 dilution and 1 plus in 1:32 dilution; serum precipitin test, 1 plus in 1:40 dilution, and spinal fluid precipitin test, 2 plus in 1:40 dilution.

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These findings were interpreted as confirming the diagnosis of coccidioidal meningitis. Skin test for coccidioidomycosis (1–10) was positive in 48 hours.

Course in Hospital: Though the headaches and dizziness increased in severity, the patient continued to be ambulatory. Actidione therapy was started on August 19. Patient received intravenously each day 30 mg. of Actidione diluted in 1,000 c.c. of 5 per cent glucose in distilled water. On one day he received only 10 mg. A total of 400 mg. of Actidione was given. The disorientation noted on admission persisted and incontinence of urine appeared. Following the medication, and for several days after it was discontinued, marked anorexia and moderate weight loss were noted. By September 9 he had developed generalized hyperreflexia, sustained ankle clonus and bilateral positive Babinski's sign, with marked ataxia. On October 11, for the first time, transient periods of increased muscle rigidity and complete loss of voluntary control of coördinated movements were noted. A second course of Actidione was started December 17. Spinal fluid examination at that time revealed a pressure of 150 mm.; 140 white cells, 25 per cent neutrophils and 75 per cent lymphocytes; protein, 495 mg. per cent; sugar, 12 mg. per cent, and sterile culture. A total of 320 mg. of Actidione was given in 16 days. There was no remarkable change in the course following therapy. Iodides were administered to tolerance for a period of four months without evident change in the clinical course. His condition remained unchanged for months. He continued to complain of headaches and to have intermittent nausea and vomiting; he appeared disoriented in all fields, and developed bilateral optic atrophy. On September 6, 1948, he developed marked stupor and vomiting and had weakness of the left extremities and hyperreflexia. There was no papilledema. Lumbar puncture examination showed a pressure of 120 mm., and Queckenstedt's test did not produce a change in the spinal fluid pressure. He died in coma September 7, 1948, nearly 15 months after admission and five and one-half years after meningitis was first demonstrated.

Postmortem Examination: The pleural cavities displayed fibrous adhesions in the apex of the left lung and in the midportion of the right lung. Each lung weighed 500 gm. Careful sectioning of the lungs showed no areas of fibrosis or cavitation. A terminal hypostatic pneumonia was found in the left lower lobe. Examination of all other thoracic and abdominal viscera revealed no pathologic changes.

The brain weighed 1,250 gm. An excess of clear spinal fluid was noted on removing the brain. The leptomeninges over the base of the brain were opaque and markedly thickened (figure 1). Many small granular tumefactions, the largest measuring 2 cm., were seen over the pons and mammillary bodies. The convolutions were flattened. The pituitary fossa was markedly enlarged. The posterior clinoid processes partially remained as a very thin layer of bone.

The ventricles were dilated to one and one-half times the normal size. There was no obstruction of the cerebral aqueduct. Many small vesicular lesions, measuring 1 mm. in diameter, gave the wall of the fourth ventricle a granular appearance.

The microscopic examination of the lungs revealed bronchial pneumonia, but no lesions suggestive of active or healed coccidioidomycosis. One small tracheobronchial lymph node showed partial granulomatous replacement. No organisms were found in the stained section.

The most conspicuous microscopic changes were those involving the leptomeninges at the base of the brain. The leptomeninges were practically replaced by dense inflammatory tissue composed of lymphocytes, plasma cells, scattered macrophages and an occasional foreign-body type of multinucleated giant cell. Inflammatory tissue was invaded by numerous fibroblasts, and in many areas there appeared to be collagenous replacement, with resultant obliteration of the arachnoidal spaces. In scattered foci the etiologic agent could be identified, but it never possessed the good histologic detail evident in the wet preparation from the meninges (figure 2)

or from the histologic picture seen in the guinea pig testicle inoculated with meningeal exudate (figure 3). Accompanying the meningitis there was a rather remarkable ependymitis, most conspicuous in the floor of the fourth ventricle and the cerebellar recesses. This heavy inflammatory mantle followed the ependymal surface and penetrated into the glial substance in a zonelike manner. The bordering blood vessels beneath the heavy mantle of the inflammatory reaction were encased with a perivascular infiltration of lymphocytes and histiocytes. The inflammatory tissue extended into the base of the choroid plexus.

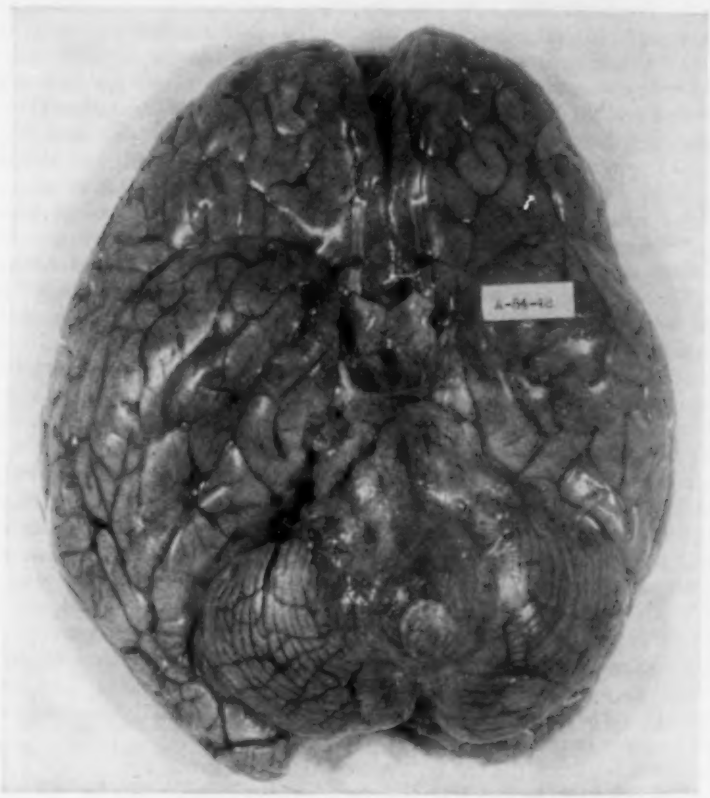

FIG. 1. Photograph of gross specimen (case 2), demonstrating the characteristically thickened and opaque meninges about the structures at the base of the brain.

Summary: This patient had developed meningitis while stationed at Camp Roberts, California, and three years later the meningitis was still present as an active infection. Therapy for a period of 15 months, including two courses of Actidione, failed to produce any significant change in the course of the disease, death finally resulting from the obstructive complications of basilar meningitis. At necropsy viable *C. immitis* were present.

Case 3. A 28 year old Negro male veteran was admitted to the McKinney Hospital on March 30, 1949, with complaints of bilateral lumbar pain and of "lumps"

over the sacrum of three weeks' duration. His illness had begun with malaise, generalized aching and lumbar back pain, followed soon thereafter by the appearance of soft, moderately tender nodules over the region of both sacroiliac joints. He had gradually developed a continuous fever, nocturia, anorexia and nervousness. Ten days prior to admission he noted swelling, pain and stiffness in the left side of the neck and left shoulder region. This was followed by the rapid appearance of fluctuant masses over the sites of the shoulder, and neck pain. One week prior to admission, a similar fluctuant mass appeared on the left chest overlying the axillary

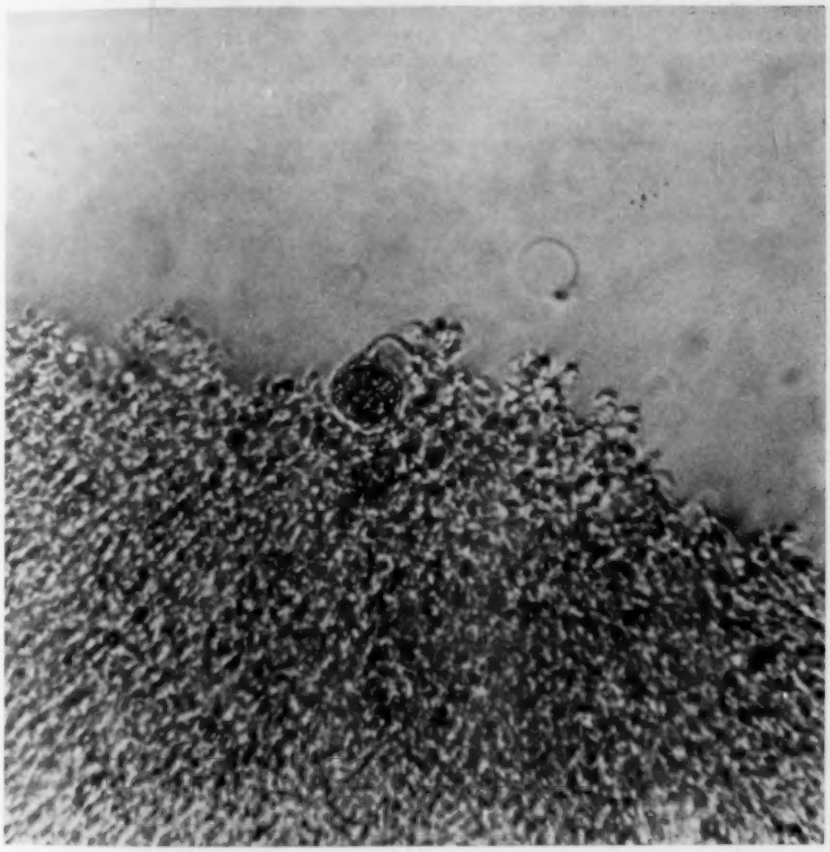

FIG. 2. Wet preparation made from meninges at necropsy (case 2), showing the thick walled endospore filled spherule of *C. immitis* (×400).

portion of the eleventh rib. Two days prior to admission he developed a diffuse throbbing headache and stiff neck that persisted until admission to the hospital. During the three weeks of illness he had a 37 pound weight loss, but except for slight nausea he had no gastrointestinal complaints. He had no respiratory symptoms.

He had served in the Navy from 1940 until 1945; most of this service was on board a destroyer in the South Pacific. Following discharge from the service, on two occasions he had been observed in hospitals in California for periods of approximately one month, once in 1947 and again in April, 1948. Those illnesses were

characterized by chills, fever and productive cough. On both occasions he had received penicillin, with questionable benefit. He resided in southern California following discharge from the service and prior to moving to Texas in February, 1949.

On physical examination he appeared acutely ill; temperature was 103° F.; pulse, 92; respirations, 20; blood pressure, 108 mm. Hg systolic and 60 mm. diastolic. Nuchal rigidity and suboccipital tenderness were present. Neurologic examination was otherwise normal. A firm fixed mass, 3 by 6 cm. in size, was found overlying and apparently attached to the axillary portion of the left twelfth rib. The left shoulder and the base of the neck on the left appeared swollen, and an area of fluctuation was present on the superior aspect of the shoulder. Both sacroiliac joints were markedly tender. There was a generalized moderate lymphadenopathy. The remainder of the physical examination, including the heart, lungs and abdomen, revealed no abnormalities.

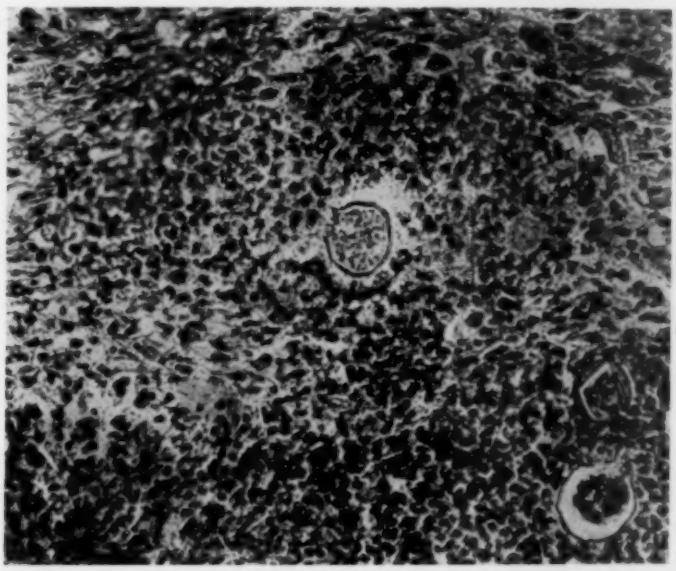

FIG. 3. Microscopic section of guinea pig testicle inoculated with meningeal exudate showing several stages of spherule development (case 2). Ruptured spherule in center of field is being invaded by neutrophils (× 400).

Laboratory Examination: Admission hemogram revealed red blood cells, 5,200,000; hemoglobin, 13 gm.; white blood cells, 13,500, with 84 per cent neutrophils, 12 per cent lymphocytes, 3 per cent monocytes and 1 per cent eosinophils. The erythrocyte sedimentation rate was 49 mm. per hour. Urinalysis was normal. Blood Kahn and Wassermann reactions were negative. Liver function tests were normal. Blood cultures were sterile. Roentgen-ray examination of the chest on admission revealed an oval parenchymal infiltration beneath the left first rib and a destructive lesion involving the sternal end of the eleventh rib. A multiloculated destructive lesion in the posteromedial aspect of the right ilium was noted on roentgen-ray.

Hospital Course: The patient was febrile on admission and remained febrile throughout the course of the illness, with frequent temperature elevations to 103° F. On aspiration of both the left shoulder mass and the right sacroiliac joint, *C. immitis* was found and identified on both direct smear and culture. Spinal fluid examination

showed a pressure of 300 mm.; 89 white cells; 98 per cent lymphocytes and 2 per cent neutrophils; protein, 67.3 mg. per cent; sugar, 57.9 mg. per cent, but no organisms were found either on direct smear or by cultural methods.

His course was slowly and progressively downward in spite of various forms of therapy. He received 2,700,000 units of penicillin, 66.5 gm. of aureomycin and 16.5 gm. of streptomycin without signs of clinical improvement. He also received sulfadiazine, acriflavine and oral undecylenic acid for prolonged periods without noticeable change. Deep roentgen-ray therapy to the involved areas for a total of 9,888 r was without benefit.

While under the above treatment the patient developed draining sinuses at the sites of aspiration of the shoulder and hip and, in addition, an osteolytic lesion in the left humerus and acromion process. These sinuses, continuing to drain purulent material, persisted until the time of death. A destructive lesion also appeared in the body of the fourth cervical vertebra, from which pus subsequently burrowed through and ruptured into the posterior pharynx. The left knee became involved in an acute arthritic process, with redness and effusion into the joint space. In May,

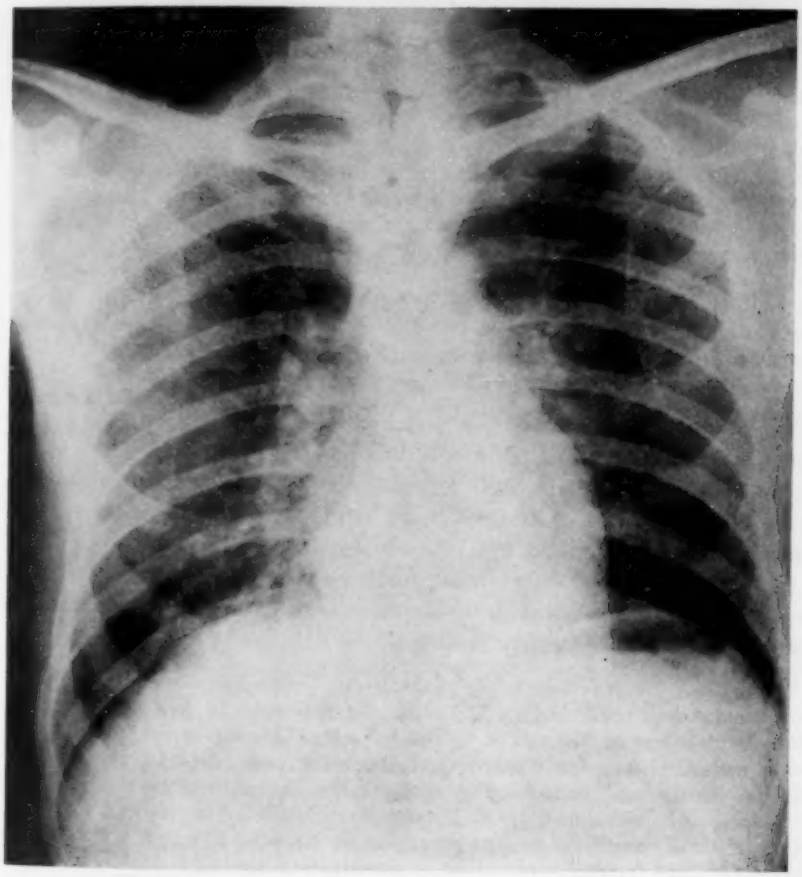

FIG. 4. Miliary type of pulmonary infiltration (case 3) developing during treatment and suggesting a hematogenous type of dissemination.

1949, he developed an extensive miliary type of parenchymal infiltration, uniformly distributed throughout both lung fields, suggesting a hematogenous type of spread (figure 4). Multiple granulating lesions appeared on the skin of the face and progressed in size in spite of treatment with undecylenic acid. During the illness he had had a variable leukocytosis ranging as high as 27,600, with polymorphonuclear cells predominating. The erythrocyte sedimentation rate was persistently elevated. He developed an anemia, the red blood cells just prior to death being 3,390,000 and hemoglobin 8.6 gm.

Except for the presence of meningismus, which may have been due to the lesion of C–4, pleocytosis in the spinal fluid and mild generalized hyperreflexia, there was no indication of central nervous system involvement until the last few weeks of his illness. On August 27 he became lethargic. On August 29 he developed convulsive movements of the face muscles, with deviation of the eyes upward and head to the right. Although he would respond to stimulation, he remained stuporous and had to be nourished intravenously until the time of death on September 5, 1949.

Postmortem Examination: There were apical adhesions bilaterally; otherwise, the pleural surfaces were smooth and glistening, and both pleural cavities contained approximately 500 c.c. of clear fluid. Each lung weighed 1,200 gm.; dispersed throughout all lobes were multiple miliary, finely granular grayish white nodules, .5 by 1 cm. in size. Granulomas were present in the moderately enlarged spleen (weight, 235 gm.) and were diffusely scattered throughout the enlarged liver (weight, 2,600 gm.). They were seen microscopically in the kidneys, adrenals and prostate. Sections of the face lesions and draining sinus tracts revealed numerous granulomas. The brain weighed 1,775 gm. The leptomeninges were slightly opaque due to thickening, particularly about the basal surface of the brain; however, no exudate was noted. Microscopically, the granulomas varied in their cellular reaction; some presented an acute exudative type of reaction in keeping with an acute hematogenous dissemination, others a more chronic type of inflammatory process. These two types of reaction were conspicuous in the brain and in the lungs. Within many of the granulomas there were large, spherical, thick-walled, highly refractile bodies, morphologically identical with *C. immitis*. The organisms were seen both intracellularly and extracellularly. Occasionally endosporulation was present (figures 5 and 6).

Summary: The onset of illness due to *C. immitis* was never accurately determined in this patient, although during both of the years preceding the appearance of the disseminated form of the disease he had suffered from febrile illnesses of the respiratory tract while living in southern California. Involvement of the meninges was demonstrated on admission to the hospital, but while he was under observation further dissemination occurred, hematogenous in type, as illustrated by the appearance of miliary pulmonary infiltration and by the necropsy findings.

Case 4. A 22 year old white male West Texas telephone lineman, was apparently quite well until August 10, 1948. At that time he had a slight cough associated with a vague discomfort in the left chest, lasting several days and disappearing under sulfonamide therapy. At about the same date he developed frontal headache, nausea and occasional vomiting. He began to note spiking afternoon fever which after about one month became continuous. After failing to respond to sulfonamide and penicillin treatment at home, he was admitted to a hospital in Beaumont, Texas, where a spinal fluid examination revealed slightly cloudy fluid, containing 396 white blood cells, 98 per cent of which were lymphocytes, 100 mg. per cent protein, and a first zone colloidal gold curve. Spinal fluid sugar was reported as "normal"; chlorides, 395 mg. per cent; smear, culture and guinea pig inoculations

of the spinal fluid failed to demonstrate organisms. On the suspicion that he suffered from tuberculous meningitis, he was given both parenteral and intrathecal streptomycin, receiving a total of 72.5 gm. He also received 9,900,000 units of penicillin. He lost 46 pounds in weight in the next six or seven weeks; fever, nausea, vomiting and headaches continued. On November 10, 1948, he was transferred to the Veterans Administration Hospital in Temple, Texas, where examination disclosed nuchal rigidity, blurring of both optic discs, congested retinal veins and generalized hyperreflexia. Spinal fluid examination revealed a clear fluid, with pressure of 420 mm.; 8 white blood cells; 225 mg. per cent protein, and sugar, 42.7

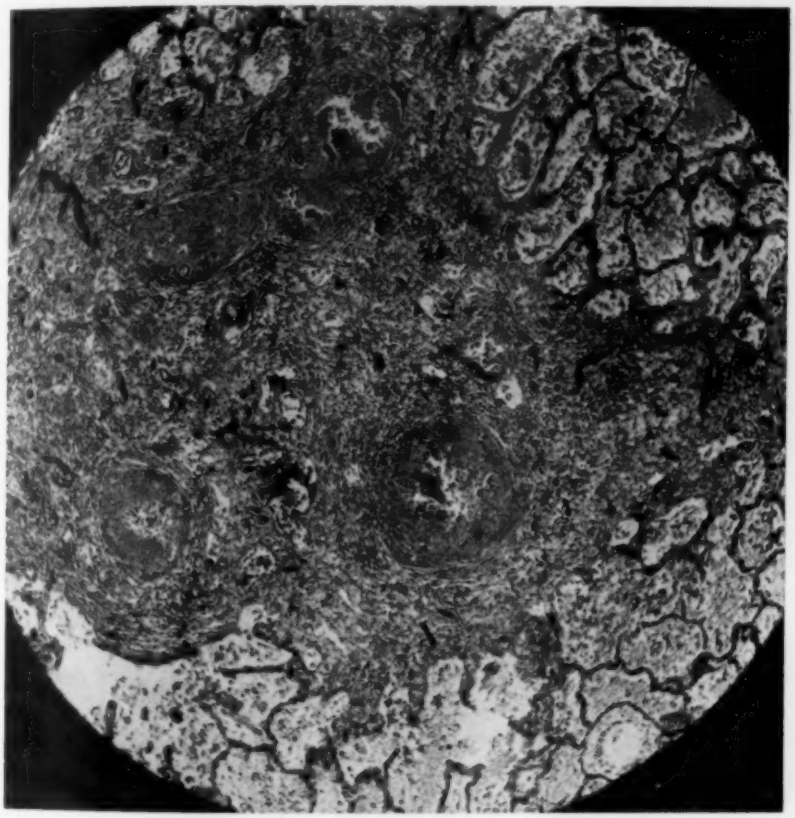

FIG. 5. Microscopic section of lungs shown in figure 4. Multiple granulomas are seen, several containing spherules morphologically identical with *C. immitis* (×50).

mg. per cent. Again no organisms were demonstrated on direct smear, cultures or guinea pig inoculation studies. The remainder of the examination, including roentgen-ray examinations of the chest, skull, paranasal sinuses and cervical spine, was within normal limits. He remained febrile during that hospitalization, with daily temperature elevations to 101° F. Repeated spinal fluid examinations demonstrated pleocytosis as high as 412 cells, 80 per cent being lymphocytes and 20 per cent neutrophils. Hemogram at that hospital showed red blood cells, 4,600,000; hemoglobin, 14 gm.; white blood cells, 5,800, with 68 per cent neutrophils, 30 per cent lymphocytes and 2 per cent eosinophils.

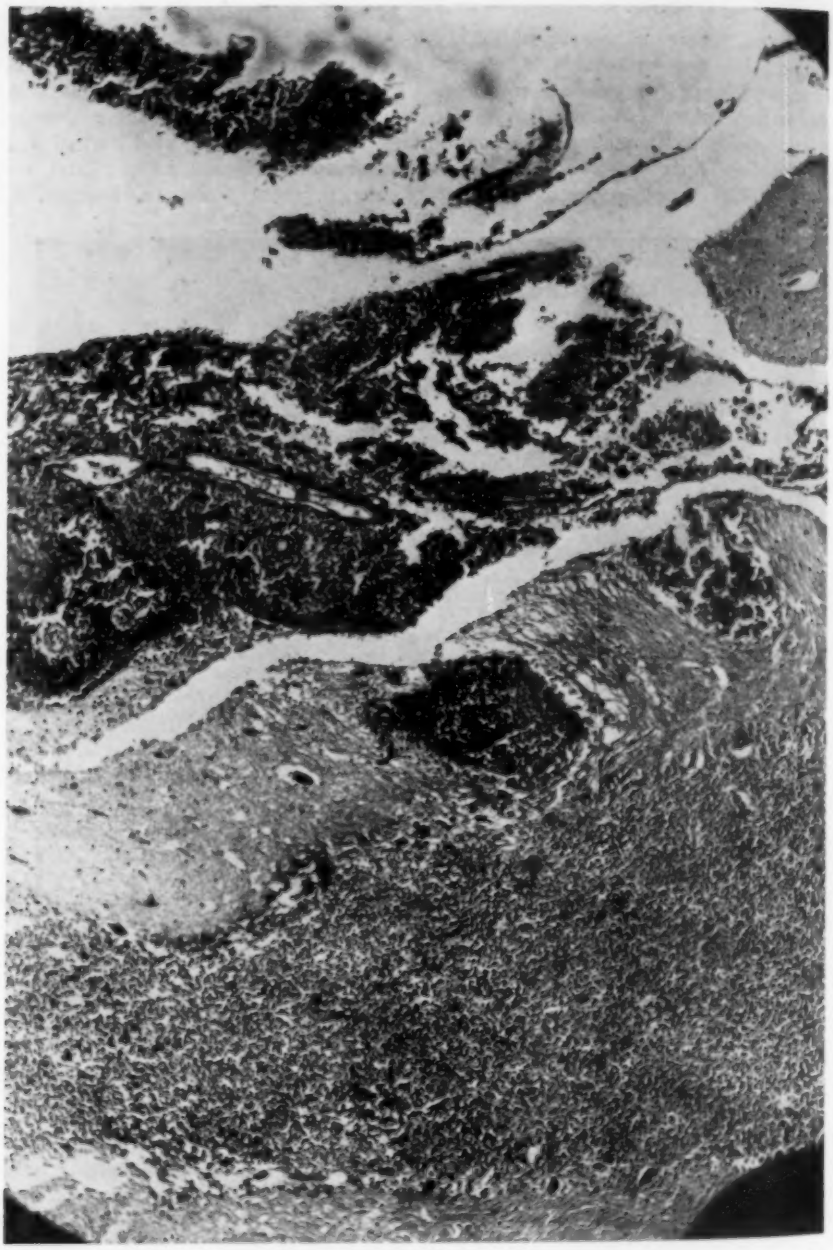

FIG. 6. Microscopic section through cerebellum (case 3). Meninges are markedly thickened by the inflammatory process, and several small abscesses are seen in the cerebellar cortex (×75).

The patient continued to receive streptomycin, both parenterally and intrathecally, and, in addition, received promin intravenously. In spite of this treatment, headache and vomiting increased, and he was transferred to the McKinney Veterans Hospital on December 1. At the time of admission to the McKinney Hospital he appeared markedly emaciated. Except for mydriasis and moderate bilateral exophthalmos, the findings were as previously noted. There were no skin lesions, adenopathy or evidence of pulmonary involvement. Chest roentgen-ray examination and other roentgen-ray studies remained normal. Repeated spinal fluid examinations continued to show pleocytosis, predominantly due to lymphocytes, with an increase in protein, a decrease in sugar, and no demonstrable organisms by any of the usual cultural methods. The first strength tuberculin (PPD) was negative, and second strength tuberculin was 1 plus positive. Tests for coccidioidal infection were not made. The hospital course was progressively downward. Nausea, vomiting, nuchal rigidity and headache persisted. The temperature curve frequently showed a low-grade elevation to 100° F.

By December 8, 1948, he had become confused and developed visual hallucinations. On December 14, bilateral Babinski reflexes and spontaneous left ankle clonus were noted. Disorientation, confusion and visual hallucinations characterized the remainder of the course. Repeated lumbar punctures failed to demonstrate a definite block, though jugular compression caused only a very sluggish rise in pressure. On December 23, after an episode of twitching of the right leg, the patient died.

Postmortem Examination: The pleura over both lungs appeared to be smooth and glistening. The lung parenchyma, with the exception of the apices, was of a dark red color, and what appeared to be aspirated vomitus was found on sectioning the lungs and on dissection of the trachea and bronchi. No areas of cavitation or nodulation were present. The tracheobronchial lymph nodes were not remarkable.

When the skull was opened the leptomeninges appeared somewhat thickened and opaque about the cerebellum and medulla. Only a slight amount of exudate was present. The brain weighed 1,350 gm.

The microscopic examination of the lungs revealed only one hyperplastic granuloma in numerous lung sections.

Sections of the brain stem revealed a very scanty exudate, diffuse in distribution, but in focal areas typical chronic granulomas were found. In an occasional granuloma a large spherical refractile body was seen, and within these bodies, in some instances, endospheres could be identified. Morphologically these bodies were typical of *C. immitis.* The granulomatous lesions were restricted to the meninges. The choroid plexus and ependyma were normal. No acid-fast organisms were found by the use of Ziehl-Neelsen stain, nor were any recovered by culture. The remainder of the postmortem findings were not significant.

Summary: The original infection in this patient was a relatively mild chest cold which appeared while he was working in West Texas. It was followed almost immediately by meningitis. The subsequent course of the disease was progressively downward, with the manifestations of a chronic meningitis showing no response to therapy. The diagnosis was made by finding the etiologic agent, *C. immitis,* at necropsy.

Discussion

The validity of the diagnosis of coccidioidal meningitis in case 1 might well be questioned. It is thought, however, that the history of pulmonary infection with cavitation and a positive dermal test to coccidioidin during

Army service, followed by the subsequent appearance of meningitis, a rising coccidioïdal complement fixation titer indicating dissemination, together with a positive coccidioidin skin test and negative tuberculin (PPD) test, make the diagnosis of coccidioidal meningitis likely beyond any reasonable doubt.

The antibiotic, Actidione,[35] used in the treatment of cases 1 and 2, is a diketone, produced by an actinomycete, and originally found in an extract of streptomycin beers. Little or no antibiotic activity was found against bacteria in 1 mg. per ml. concentration; however, considerable fungicidal effect was noted for many yeast organisms. Acute toxicity experiments on Actidione were summarized by Bond in 1946 and 1947 and by Brooks in 1947.[36] Actidione has been used clinically with reported success in the treatment of infections in man due to *Blastomycosis dermatitidis, Candida albicans* and *Cryptococcus neoformans.*[36]

The remarkable clinical response that followed Actidione in case 1 was interpreted as a remission in the disease process, although it could represent an actual recovery from the infection. Complete recovery seems unlikely, however, since the spinal fluid examination seven months following treatment still showed a pleocytosis, increased protein and low sugar. It is known that survival for long periods occurs with coccidioidal meningitis, death ultimately resulting from complications incident to a cerebrospinal fluid block. Only one case of possible recovery from coccidioidal meningitis could be found in the literature,[7] and that case was reported as a two year and seven month survival rather than as a recovery. Our case was doing well when last heard from (February 5, 1950), and so represents a three-year survival. Disseminations having occurred three years after the original infection would tend to support the theory of late dissemination.[1] This case was also remarkable in that dissemination apparently followed cavitary pulmonary disease.

The second case appears to be clearly one of early dissemination. The clinical course and serologic tests are in accord with this diagnosis. It should be remembered that this patient survived five and one-half years after the onset of meningitis, indicating that long survival periods can be expected. The etiologic agent, *C. immitis,* was demonstrated by tissue, cultural and animal inoculation studies from the material obtained at necropsy. The presence of viable *C. immitis* after the patient had had two courses of Actidione therapy makes the therapeutic effectiveness of Actidione doubtful. Failure of the drug to cross the tissue barriers of the central nervous system may have been responsible for its failure in this case, since, when added to cultures of *C. immitis,* Actidione has been shown to have fungistatic properties.[35] Death in case 2 was undoubtedly caused by progressive internal hydrocephalus, secondary to basilar meningitis.

Case 3 is also an example of the disseminated form of coccidioidomycosis with meningitis. The widespread involvement in this case is compatible with a hematogenous type of dissemination, and may represent another example of late dissemination. The chest roentgenogram showed quite

clearly the disseminated process in the lungs, which was identical with that seen in miliary tuberculosis. Undecylenic acid therapy, used in the treatment of this patient, was without benefit.

Case 4 demonstrates the problem that may be encountered in the diagnosis of the chronic form of coccidioidal meningitis. The patient had been considered to have tuberculous meningitis and had received streptomycin therapy. Even at the time of necropsy the patient was thought to have tuberculosis, and cultural studies for coccidioidomycosis were not done. The microscopic sections, however, revealed the coccidioidal organisms, and no acid-fast organisms could be demonstrated. This case stresses the importance of considering coccidioidomycosis in any case of chronic meningitis for which a specific causative organism has not been identified. Serologic studies and skin testing with coccidioidin would undoubtedly have clarified the diagnosis in this patient.

Summary

Four cases of coccidioidal meningitis are reported, with necropsy findings in three of the cases.

One individual apparently underwent remission following the use of the antibiotic Actidione. However, the effectiveness of Actidione could not be evaluated in this study. Only one other remission of similar duration could be found in a review of the literature.

Two of the subjects reported are probably examples of so-called late dissemination.

One patient survived five and one-half years after the development of coccidioidal meningitis, indicating that long survival in this disease is possible.

The importance of considering coccidioidomycosis in the diagnosis of chronic meningitis is stressed.

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INTERMITTENT AND TRANSIENT BUNDLE BRANCH BLOCK: A CLINICAL AND ELECTROCARDIOGRAPHIC STUDY *

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INTRODUCTION

SHORTLY after the recognition of the pattern of bundle branch block in the animal and human electrocardiogram,[1] it was demonstrated that such patterns were often associated with lesions of one or both branches of the bundle of His.[2] Many investigators demonstrated that the presence of bundle branch block in the electrocardiogram was generally associated with a diseased heart.[3, 4] Although many reports of bundle branch block have appeared in otherwise normal persons,[5, 6] the majority of patients showing this pattern have definite cardiac involvement.[7, 8]

The nature and significance of transient or paroxysmal bundle branch block were not clearly appreciated until 1930, when a differentiation was made between transient bundle branch block and the Wolff-Parkinson-White syndrome.[9] The latter is not often associated with demonstrable cardiac involvement, whereas transient bundle branch block is usually associated with a diseased heart. Comeau, Hamilton and White [10] in their review of the literature were able to collect 77 cases of transient bundle branch block, only six of which did not have evidence of organic heart disease. The presence of such involvement probably rendered the bundle of His and its branches more susceptible to changes in conduction in the presence of anoxemia,[11, 12] change in heart rate,[11, 13, 14] infection [15, 16] or vagal effects.[14, 17, 18]

Some observers have likened the changes in conduction in the bundle branches to those occurring in the A–V node.[17, 19, 20] However, owing to the peculiar anatomic relationship of the bundle and its branches, the different degrees of delay in conduction as encountered in the A–V node are not as readily ascertained in the bundle branches.

The present report deals with a selected group of cases, some of rather rare and unusual occurrence, demonstrating many aspects of changes in conduction in the bundle branches as they appear in the human electrocardiogram. This group includes cases of bundle branch block, occasionally of several years' duration, with later reappearance of normal conduction; unstable right bundle branch block of the Wilson type; an interesting case of

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partial left bundle branch block with varying degrees of complete and incomplete block, and instances in which bundle branch block could be induced or abolished. The occurrence of transient or paroxysmal bundle branch block or of normally conducted QRS complexes in the presence of bundle branch block can be better evaluated when the available experimental and clinical data are considered. The many varieties of such cases, while differing in detail, actually present an essentially homogeneous group when carefully analyzed.

Material

The cases included in this report consist of 12 persons who at one time or another showed transient or intermittent bundle branch block. In seven of these cases, various procedures were carried out in an effort to cause either bundle branch block or normal conduction to appear, depending upon the control record. These maneuvers included the "2-step" exercise test,[21] anoxemia test,[22] breathing of 100 per cent oxygen for 20 minutes, changes in posture, respiratory maneuvers, inhalation of amyl nitrite, and carotid pressure. In several of the patients, esophageal records were obtained by methods described previously.[23]

Results

The cases have been divided into several groups for the purpose of discussion and analysis.

I. *Premature ventricular complexes simulating normal conduction in the presence of bundle branch block:*

Case 1. This 45 year old white man had rheumatic fever at the age of 12 and has had cardiac murmurs since that time. For the last few years, there has been some restriction of activity and he has been taking digitalis. Physical examination revealed signs of aortic stenosis and insufficiency and mitral insufficiency. His blood pressure was 130/100 mm. of Hg. Fluoroscopic examination revealed cardiac enlargement with some widening of the aorta.

Electrocardiograms (figure 1): Regular sinus rhythm with an R–R interval of 0.70 second was present with left bundle branch block and occasional premature ventricular complexes. The QRS of the left bundle branch block was 0.16 second in duration. The premature ventricular complexes were of much shorter duration than those of left bundle branch block. The first premature complex in Lead I was 0.12 second in duration and followed the preceding left bundle branch block complex by 0.56 second; the second premature complex in Lead I was 0.09 second in duration and followed the preceding complex by 0.68 second. The duration or timing of the third premature complex was the same as of the first.

Comment: Normally the impulse, after traversing the A–V node, is conducted with great rapidity over the bundle of His and its branches.[24] The septum is activated from both the left and right bundle branches. In the presence of blocked conduction in the left bundle branch, the impulse has to reach the left side of the heart by traversing the musculature of the septum until it reaches the conductive system distal to the block. This muscular

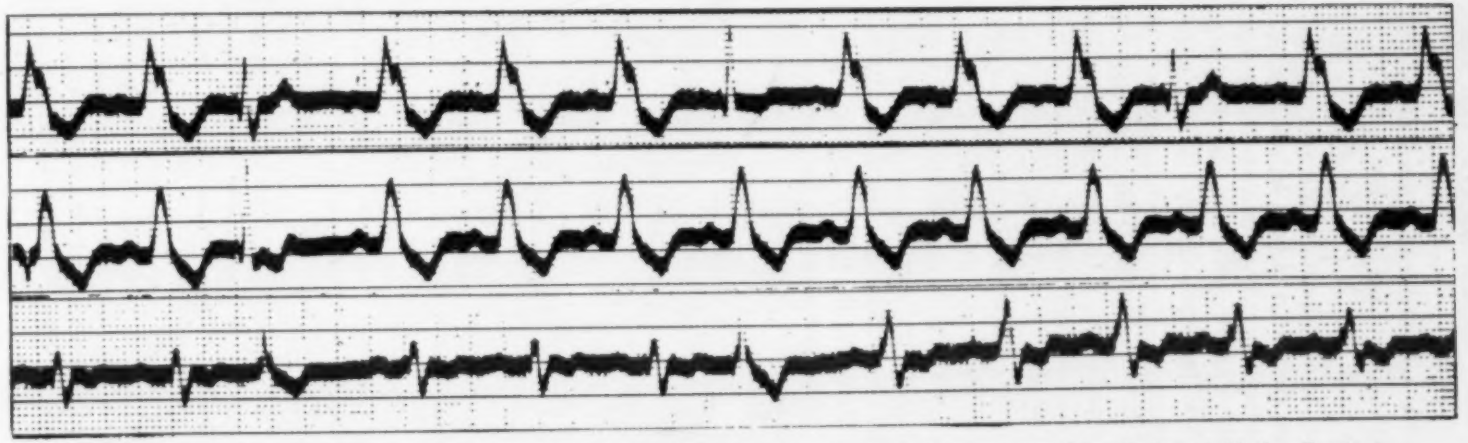

FIG. 1. (Case 1) Premature ventricular complexes simulating normal conduction in the presence of bundle branch block. See text.

spread accounts for the widened and slurred QRS complex.[25] The occurrence of premature beats of normal or nearly normal duration in the presence of left bundle branch block may be explained by the discharge of an irritable focus in the septum, with activation of both ventricles occurring concurrently or by the simultaneous discharge of both bundle branches.[26, 27] In the above case, the premature complex which occurred 0.68 second after the preceding beat was of shorter duration than the first and third premature complexes in Lead I. This can best be explained by the assumption that the irritable focus was in or near the left bundle branch and that activation of the right ventricle occurred at the usual time and through the normal pathway.

Wilson and Herrmann [28] have demonstrated that the normal ventricular complex can be considered as being composed of a dextrocardiogram and levocardiogram. They also showed that any significant asynchronism in the activation of either ventricle will prolong the QRS interval and hence result in the pattern of bundle branch block. To demonstrate this concept, both bundle branches in a dog's heart were severed and each ventricle was stimulated separately. If the ventricles were simultaneously stimulated, an essentially normal QRS complex was recorded. When one ventricle was stimulated later than the other, the QRS complex was prolonged to an extent dependent upon the elapsed time between the stimulation of the ventricles.

In the above case, the pattern of left bundle branch block is due to asynchronism in the stimulation of each ventricle, the left being stimulated much later than the right. The premature ventricular complex of 0.08 second probably represents the simultaneous activation of each ventricle, while the premature complexes of longer duration represent slight asynchronism in the activation of the ventricles.

II. *Partial bundle branch block* (QRS complexes of varying duration):

Case 2. This 66 year old white man was admitted on September 3, 1945, with complaints of abdominal pain, diarrhea with watery non-bloody stools, and vomiting of three days' duration. He also had a nonproductive cough and a temperature of 101 to 102° F. of six days' duration. The patient was acutely ill and dehydrated on admission. There were decreased breath sounds and numerous fine and medium moist râles at both lung bases. Vocal fremitus was increased at the right base. The blood pressure was 120/70 mm. of Hg; temperature, 102.2° F.; pulse, 100. The fundus was normal. Laboratory data revealed a one plus guaiac test in the stools; erythrocyte sedimentation rate, 19 mm. per hour; hemoglobin, 14.5 gm.; leukocytes, 4,700 per cu. mm. of blood, with a marked shift to the left. A roentgenogram of the chest revealed a pleural effusion on the right side, with unusual infiltration throughout both lung fields. Stool and nose cultures were positive for *Salmonella anatum.* Blood agglutination against this organism was 1:640. Blood cultures were negative. A Wassermann test was negative. His past history was insignificant except for an operation for peptic ulcer 30 years ago.

The patient was treated with intravenous fluids, blood transfusion, penicillin and sulfasuxidine. He had a rather stormy course for a few weeks, and at one time developed urinary retention and, later, incontinence of urine and feces. At that time, spinal fluid examination revealed a spinal fluid protein of 138 mg. per cent but was otherwise negative. On September 7 the patient was slightly cyanotic. The leukocyte

count on September 10 was 12,400 per cu. mm. and on September 11, 29,400 per cu. mm. On September 19 he was given 1.4 mg. Digitalis Nativelle and 1 c.c. Mercuhydrin and, because of dyspnea and cyanosis, was placed in an oxygen tent. On September 23 the heart sounds were distant, and a few days later adventitious systolic and diastolic sounds were heard over the precordium. Following the initial dose of 1.4 mg., the patient was given 0.1 mg. Digitalis Nativelle daily. He made a slow recovery and was discharged markedly improved on November 15.

Electrocardiograms (figure 2): All tracings revealed regular sinus rhythm. On September 4 the R–R interval was 0.54 second, and patterns of left bundle branch

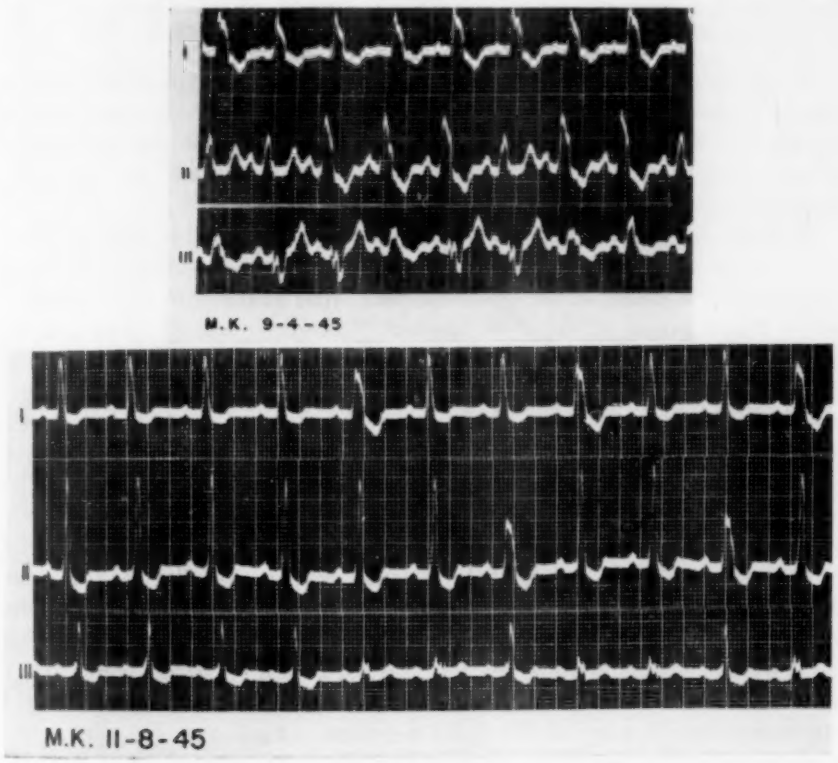

FIG. 2. (Case 2) Partial bundle branch block. See text.

block of two varieties were present. In all leads, complexes of left bundle branch block of longer and shorter duration were intermingled. The QRS complexes were 0.14 to 0.15 and 0.11 to 0.12 second in duration, respectively. The complexes of shorter duration were of low amplitude, with upright T waves in Lead II, and consisted of an R wave with inverted T waves in Lead III. The wider complexes were followed by inverted T waves in Lead II and upright T waves in Lead III, and consisted of an RS pattern in Lead III. All complexes were slurred and notched and preceded by a P wave and identical P–R intervals. On September 7 at an R–R interval of 0.69 second the record exhibited left bundle branch block with complexes of 0.16 second in duration which resembled the wider complexes in Lead I on September 4. On September 20 the R–R interval was 0.66 second and the QRS complexes were lower

in amplitude and measured 0.12 second in duration. They resembled the wider complexes on September 4, with the exception that the complex in Lead III was M-shaped. On September 28, with an R–R of 0.72 second, the QRS complexes were 0.12 second in duration and were followed by diphasic T waves in Lead I. On October 10 the QRS complexes were of slightly higher amplitude than on September 28, and the T waves were inverted. On October 19, with an R–R interval of 0.68 second, the record exhibited QRS complexes of high amplitude of 0.08 to 0.09 second in duration and inverted T waves. No complexes characteristic of left bundle branch block were present. On November 8 the electrocardiogram revealed apparently normal conduction and occasional QRS complexes which were 0.12 second in duration and characteristic of left bundle branch block. These complexes occurred every third, fourth or fifth beat, or in paroxysms.

Comment: This case demonstrates a very infrequent type of partial bundle branch block. The initial record revealed ventricular complexes of varying degrees of left bundle branch block. The last record was that of apparently normal conduction, with ventricular complexes of left bundle branch block occurring intermittently.

Partial left bundle branch block has been compared by some authors to partial A–V block.[17, 19, 20] Delay in conduction in a bundle branch should result in prolongation of the QRS complex, just as delay in A–V conduction causes prolongation of the P–R interval.[28] Bundle branch block analogous to 2:1, 3:1 or other degrees of A–V block theoretically should result in a series of QRS complexes of normal duration occurring at regular intervals with QRS complexes of typical complete bundle branch block. However, the demonstration of such an instance is difficult of proof because of the peculiar anatomic relationship of the bundles in the human heart. It is quite possible that the impulse in the affected bundle, while apparently delayed, may still activate the ipsilateral ventricle, although the impulse from the contralateral side has already invaded a large portion of the septum. Hence, the completeness of the bundle branch block is difficult to state since neither the duration of the QRS complex nor its configuration in routine leads gives the desired information. Bundle branch block comparable to the Wenckebach phenomenon in A–V conduction should be evidenced by progressive lengthening of the QRS complex. However, the time interval in which an increment to the duration of the QRS complex can occur is so limited (0.03 second) that such a condition is not frequently seen.[17, 29] Routine electrocardiography is not usually sufficient for the recognition of this pattern. The above facts have been pointed out by Wilson and Herrmann,[28] Herrmann and Ashman [17] and others.[19, 29]

It is quite probable that the above case is comparable to partial A–V block. The varying durations of the QRS complex would indicate varying delays in conduction in the affected left bundle branch. In the last record the QRS complex of even the apparently normally conducted ventricular impulses may represent partial delay in the left bundle branch. The wider QRS patterns of left bundle branch block are apparently typical of complete left bundle branch block. However, even in these instances, the ipsilateral

ventricle may finally be activated by the left bundle branch after initial delay in this bundle.

III. *Transient bundle branch block:*

Case 3. A 57 year old white man was admitted to The Mount Sinai Hospital on September 28, 1949, with the chief complaints of abdominal pain, exertional dyspnea, angina on exertion and intermittent claudication and weakness. He had lost considerable weight. The past history revealed pneumonia and pleurisy five years ago and 20 years ago, respectively. On examination, the patient was extremely pale; his heart was not enlarged to percussion. A soft systolic murmur was present at the apical area and the blood pressure was 117/68 mm. of Hg. Roentgenograms revealed a filling defect in the jejunum. He was operated upon on October 11, and an adenocarcinoma of the jejunum was resected. Metastases to lymph nodes were found. At the time of admission, the laboratory data were as follows: 6 gm. hemoglobin; erythrocytes 2,300,000 per cu. mm. of blood; leukocytes, 11,400 per cu. mm.; no free gastric acid; 3 plus cephalin flocculation; blood urea nitrogen, 14 mg. per cent, and 1 plus albumin in the urine. The patient was given many transfusions, until his hemoglobin was 12 gm. by the day of operation. He made a good recovery following the operation. On February 25, 1950, on reëxamination, his heart was normal and his blood pressure was 125/80 mm. of Hg. The patient was asymptomatic at that time.

Electrocardiograms: The records taken on September 29, 1949, revealed regular sinus rhythm with an R–R interval of 0.72 second, and a pattern typical of left bundle branch block (figure 3A). The QRS complex was 0.12 second in duration and slurred and notched. On February 25, 1950, regular sinus rhythm was present with normally conducted ventricular complexes. The R–R interval was 0.80 second, and the QRS complexes were 0.05 to 0.06 second in duration (figure 3B). Esophageal electrocardiograms demonstrated a normal ventricular transitional pattern of the qR variety.[20] The patient performed the double "2-step" exercise test, inhaled amyl nitrite and was given an anoxemia test. With amyl nitrite there was a drop in blood pressure to 80/70 mm. of Hg and an increase in heart rate to an R–R interval of 0.68 second. No bundle branch block pattern appeared. The exercise and anoxemia tests were normal.[21, 22]

Case 4. A 58 year old dentist was first seen in May, 1946, with the chief complaint of having felt a lump in his throat for one year. The patient also gave a history of dyspnea on climbing stairs, substernal burning sensation on walking and palpitation on effort. The blood pressure was 120/70 mm. of Hg. Examination at that time revealed a very nervous person with a heart rate of 60 per minute with occasional premature contractions. There was no evidence of cardiac enlargement on percussion and the heart sounds were distant. During that year he had had several attacks of angina pectoris, which were relieved by nitroglycerin. The patient was next seen on March 6, 1950, and was found to have left ventricular hypertrophy on fluoroscopic examination. The attacks of angina had also become more severe and frequent, and were still relieved by nitroglycerin.

Electrocardiograms (figure 4): On December 7, 1945, the record revealed regular sinus rhythm with QRS complexes of normal duration. Following exertion a series of complexes of left bundle branch block pattern appeared. In the electrocardiograms on September 20, 1946, and May 25, 1948, there was persistent left bundle branch block with notched QRS complexes 0.13 to 0.14 second in duration. On November 9, 1948, the record again demonstrated left bundle branch block with depression of the RS–T segments and diphasic T waves. On March 6, 1950, normal conduction was present, with QRS complexes of 0.08 second duration. The pattern was that of left ventricular hypertrophy, and there was no evidence of left bundle branch block.

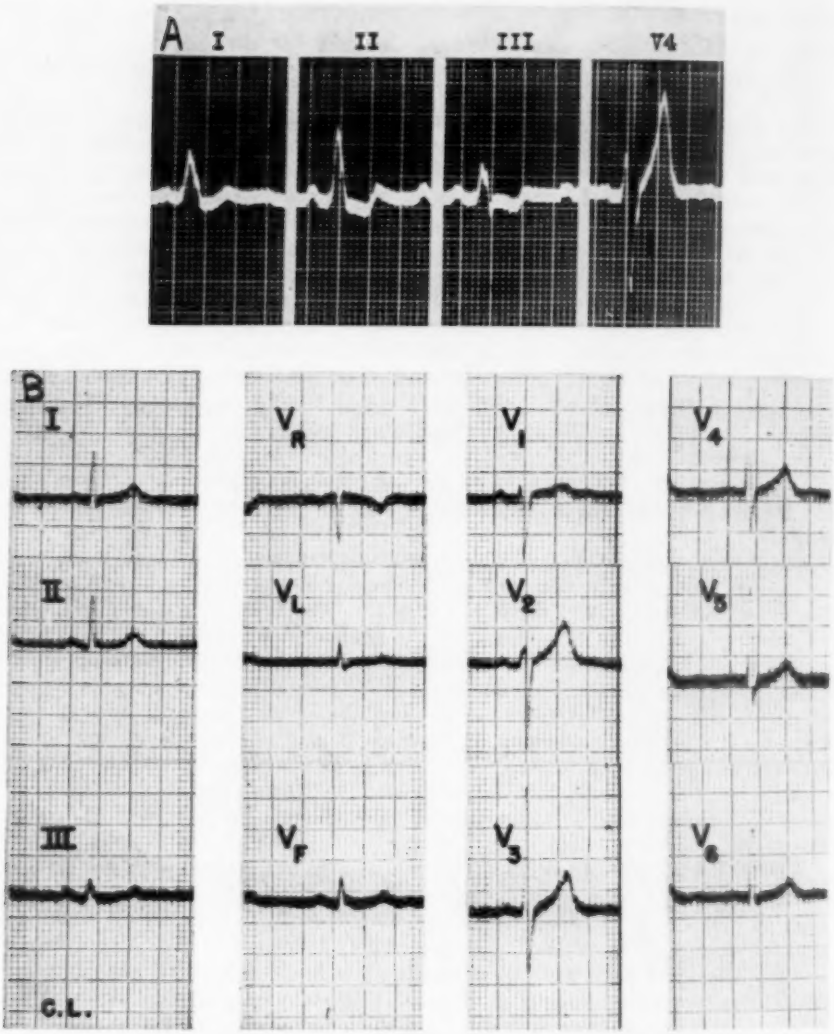

FIG. 3. (Case 3) Transient bundle branch block. See text.

Case 5. This case has been described in more detail elsewhere.[81] The patient was a 43 year old white woman with the chief complaints of constrictive substernal pain and palpitation. The pain usually occurred following effort and was usually relieved by either rest or 0.45 mg. of nitroglycerin taken sublingually. The pain radiated to the throat and down the inner aspects of both arms. Her past history revealed that she had had lobar pneumonia in 1942 and had recovered following sulfadiazine therapy. In 1944, the patient had had a salpingo-oöphorectomy and several cervical biopsies. In May, 1948, a right mastectomy for chronic mastitis was performed. The heart and lungs have been essentially normal on physical examination, fluoroscopic and roentgenologic examination for the last eight years. The blood cholesterol has ranged between 218 and 330 mg. per cent. Urine has been

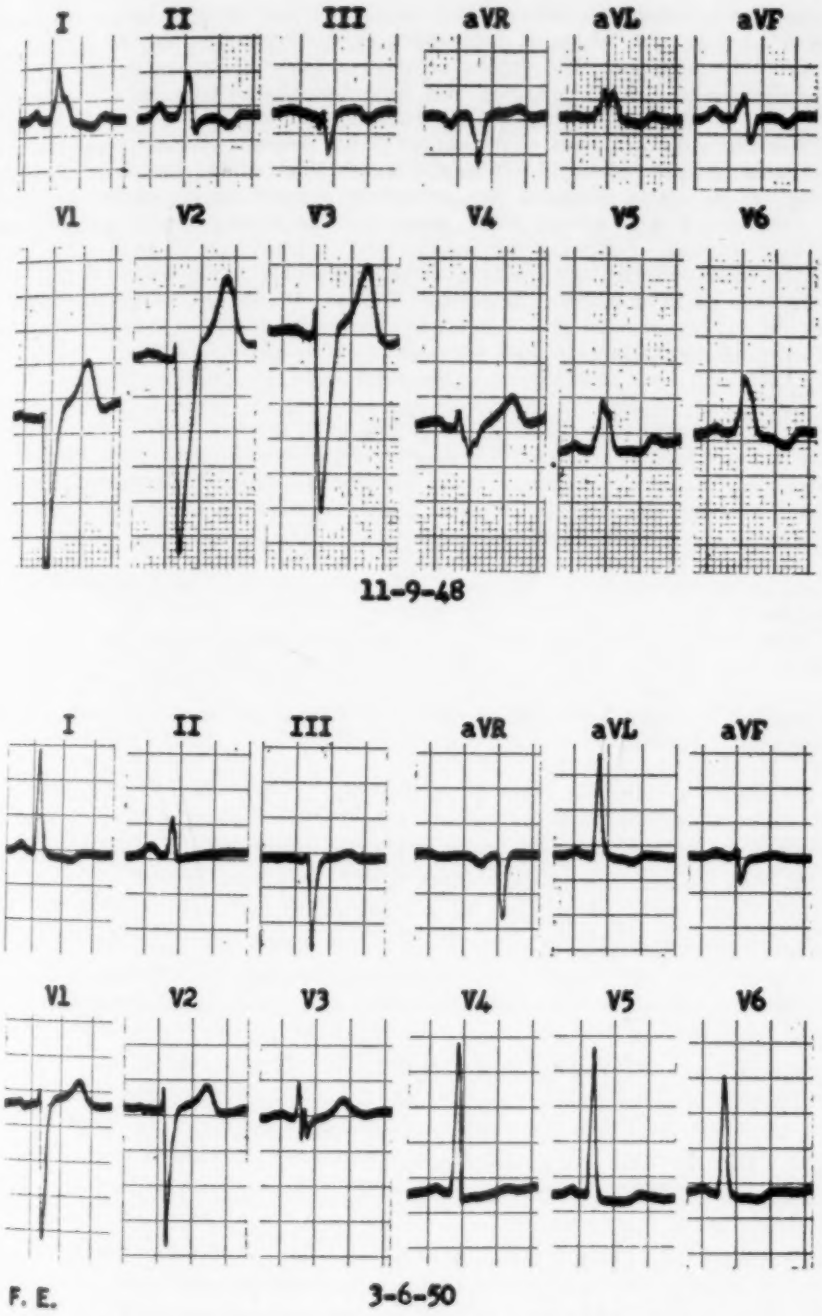

FIG. 4. (Case 4) Transient bundle branch block. See text.

negative for reducing substances. The hemoglobin was 64 per cent; erythrocytes, 3,500,000 per cu. mm. of blood, and leukocytes, 6,000 per cu. mm.

Electrocardiograms: The details of this patient's electrocardiograms may be found elsewhere.[31] The record was first noticed to change transiently from normal conduction to left bundle branch block following an exercise test in April, 1947. In 1950, during several visits of the patient to the hospital, various procedures were carried out to induce transient left bundle branch block. The procedures included a "2-step" exercise test, anoxemia test, inhalation of amyl nitrite, nitroglycerin, 0.45 mg. sublingually, and carotid sinus pressure. The resting control records were essentially normal. Following the exercise test or inhalation of amyl nitrite, transient left bundle branch block appeared for varying periods whenever the R–R interval fell into the range of 0.50 to 0.57 second. Normal conduction reappeared when the R–R interval became 0.60 to 0.67 second. The esophageal electrocardiograms were typical of left bundle branch block whenever such complexes appeared. Transitional QRS complexes were also present in the esophageal electrocardiograms.[31]

Case 6. A 64 year old white man was admitted to The Mount Sinai Hospital on March 7, 1950, with the chief complaints of orthopnea, paroxysmal nocturnal dyspnea and angina on exertion. On admission the patient was dyspneic and slightly cyanotic. The heart was enlarged to the left, and soft systolic murmurs were present at both the aortic and the apical areas. A gallop rhythm was present and râles were heard at both lung bases. The blood pressure was 112/70 mm. of Hg. He was given 1.2 mg. of digitoxin and 1 c.c. of Mercuhydrin on the day of admission. By March 10 the patient was markedly improved. The gallop rhythm had disappeared and no râles were heard.

Electrocardiograms: On March 7 regular sinus rhythm was present with an R–R interval of 0.62 second and there were QRS complexes typical of right bundle branch block of the Wilson type of 0.12 second duration. On March 10 normal conduction was recorded with QRS complexes of 0.06 second duration. The R–R interval was 0.72 second.

Comment: The four cases above, three of left bundle branch block and one of right bundle branch block of the Wilson type, are characterized by the presence of heart disease and the transient appearance of bundle branch block. In Case 5, the appearance of QRS complexes typical of left bundle branch block could be ascribed to a more rapid heart rate. This case has been discussed in detail elsewhere.[31] In Case 3, left bundle branch block was associated with severe anemia and angina pectoris, but normal QRS complexes appeared when the patient was operated upon and the anemia treated with transfusions. Case 6 was admitted in failure, with right bundle branch block of the Wilson type present. With improvement in his general condition and the disappearance of failure, the right bundle branch block was replaced by QRS complexes of normal duration. In Case 4, with angina pectoris and left ventricular hypertrophy, the transiency of the left bundle branch block pattern could not be definitely ascribed to any simultaneous clinical manifestation.

Many factors can probably precipitate transient bundle branch block.[32] Such factors include tachycardia, anoxemia, anemia, myocardial infarction[33] and metabolic disturbances. Some investigators have stated that transient bundle branch block is associated with a more favorable prognosis than chronic bundle branch block,[17] and may be present in persons with less

severe forms of heart disease. From a review of the literature since the publication of the paper of Comeau, Hamilton and White,[10] we have been able to collect 82 cases of transient bundle branch block, in only six of which there was no apparent heart disease. In addition, among these 82 cases there were four with hyperthyroidism [34, 35, 36, 37] and bundle branch block which disappeared following the amelioration of the hyperthyroidism; one with myasthenia gravis [38] and bundle branch block, with disappearance of the conduction defect following the treatment of the myasthenia gravis, and two with bundle branch block subsequent to the administration of drugs of the quinine group.[39, 40] In the latter two cases, QRS complexes of normal duration occurred when the drug was stopped.

Thus, in these four cases of the present report, as well as in those reported in the literature previously, it is apparent that the presence of cardiac involvement renders the conductive system more susceptible to impairment. The additional factors of tachycardia, anoxemia, anemia, myocardial infarction and metabolic disturbances can produce bundle branch block in such hearts during the period in which they are present. The amelioration or cessation of such concurrent conditions may be sufficient to nullify the effects of the precipitating factors.

IV. *Normally conducted ventricular complexes in the presence of left bundle branch block* (QRS complexes of normal duration occurring in the same record as left bundle branch block):

Case 7. A 57 year old white woman was admitted on December 22, 1947, with the complaints of fatigue, pain in both knees and swelling of both legs. Nine weeks prior to admission she had had an upper respiratory infection with substernal pain and cough, and for several weeks had had anorexia and polyuria. Also, the patient was told at one time that she had a bundle branch block and an irregular pulse. Examination revealed a chronically ill woman whose blood pressure was 135/80 mm. of Hg. There was a small nodule palpated in the suprasternal fossa. The heart was enlarged to the left and a soft systolic apical murmur was heard. The cardiac rhythm was regular except for occasional coupling. Examination of the fundus revealed an increased light reflex and dilated venules. Neurologic examination was negative. Roentgenograms of the bones revealed generalized osteoporosis. The urine was of low specific gravity and there was a 3 plus Sulkowitch reaction. The urinary function tests were essentially normal. The blood calcium ranged from 12 to 16 mg. per cent; phosphorus, 2.1 to 2.8 mg. per cent; alkaline phosphatase, 11 to 18 B.U.; hemoglobin, 10.5 gm.; leukocytes, 13,700 per cu. mm. of blood; cholesterol, 243 mg. per cent; fasting blood sugar, 119 mg. per cent. The Wassermann reaction was negative; blood urea nitrogen was 9 mg. per cent, and total protein, 7.1 gm. An operation was performed on December 30 and a parathyroid adenoma was removed. She was given 30 units of parathormone and intravenous glucose after the operation. Two days postoperatively the blood calcium was 9.2 mg. per cent. A positive Chvostek's sign was elicited on January 11, 1948, at which time the blood calcium was 6.2 mg. per cent. The patient was given intravenous calcium, with good results, and was started on 0.625 mg. AT 10 daily. The Sulkowitch test was negative at this time, and the blood pressure was 150–160/90 mm. of Hg. On January 25 the blood calcium was 8.8 mg. per cent. On February 11 the Bauer-Aub diet was given to the patient, and 240 mg. of calcium were subsequently present in 5,190 c.c. of urine. The

patient was discharged and maintained on 1.25 mg. of AT 10 and 30 gm. of calcium gluconate orally. At the time of the last examination (March 8, 1950), she was doing well on AT 10 and calcium gluconate.

Electrocardiograms: Regular sinus rhythm was present in every record. On December 23, 1947, the electrocardiogram revealed an R–R interval of 0.77 second, with QRS complexes of 0.07 second duration. Left axis deviation was present. The QT interval was 0.40 second. The T waves were inverted in Leads CF_1–CF_3 and of low amplitude in CF_4–CF_6. On December 30 the electrocardiogram exhibited complexes of normal conduction alternating with those of left bundle branch block, the latter being 0.15 to 0.16 second in duration (figure 5A). The electrocardiograms on January 2, January 5, January 20 and February 8, 1948, revealed normally conducted

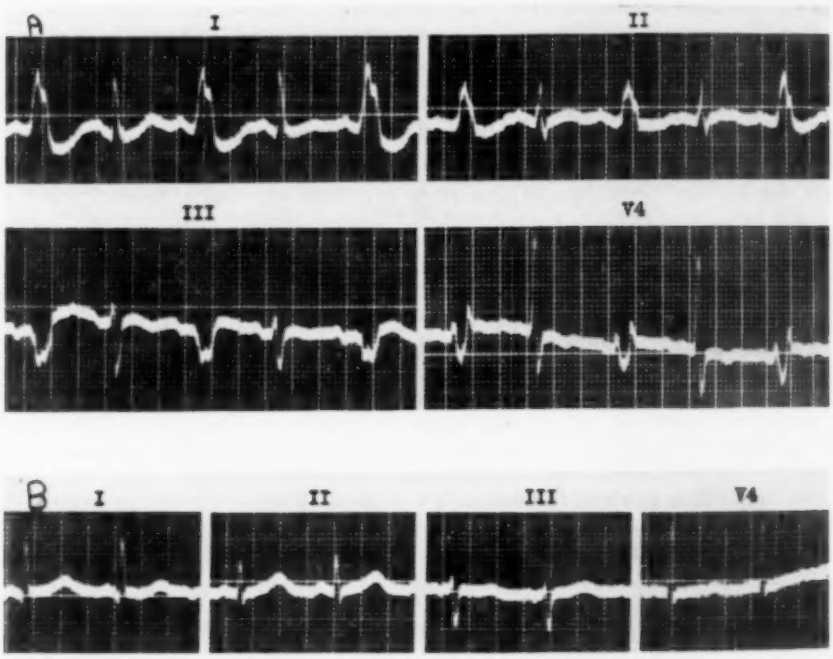

FIG. 5. (Case 7) Normally conducted ventricular complexes in the presence of bundle branch block. See text.

QRS complexes (figure 5B). The T waves were inverted in Leads V_1–V_3 and flat in V_4–V_6. On February 2, 1950, only the pattern of left bundle branch block with QRS complexes of 0.15 second duration was present, with an R–R interval of 0.72 second. On February 17 left bundle branch block was present. However, during the taking of the record (direct writing three channel Technicon Cardiograph), alternating left bundle branch block and normally conducted QRS complexes appeared for 15 seconds. The R–R interval remained constant at 0.56 second (figure 6). On March 8 several procedures were carried out. Amyl nitrite was inhaled, with the R–R interval decreasing to 0.54 second. No change was noticed in the ventricular complexes. The breathing of 100 per cent oxygen for 20 minutes had no effect on the configuration of the QRS complex. Carotid pressure was applied eight times. The control record revealed left bundle branch block with occasional

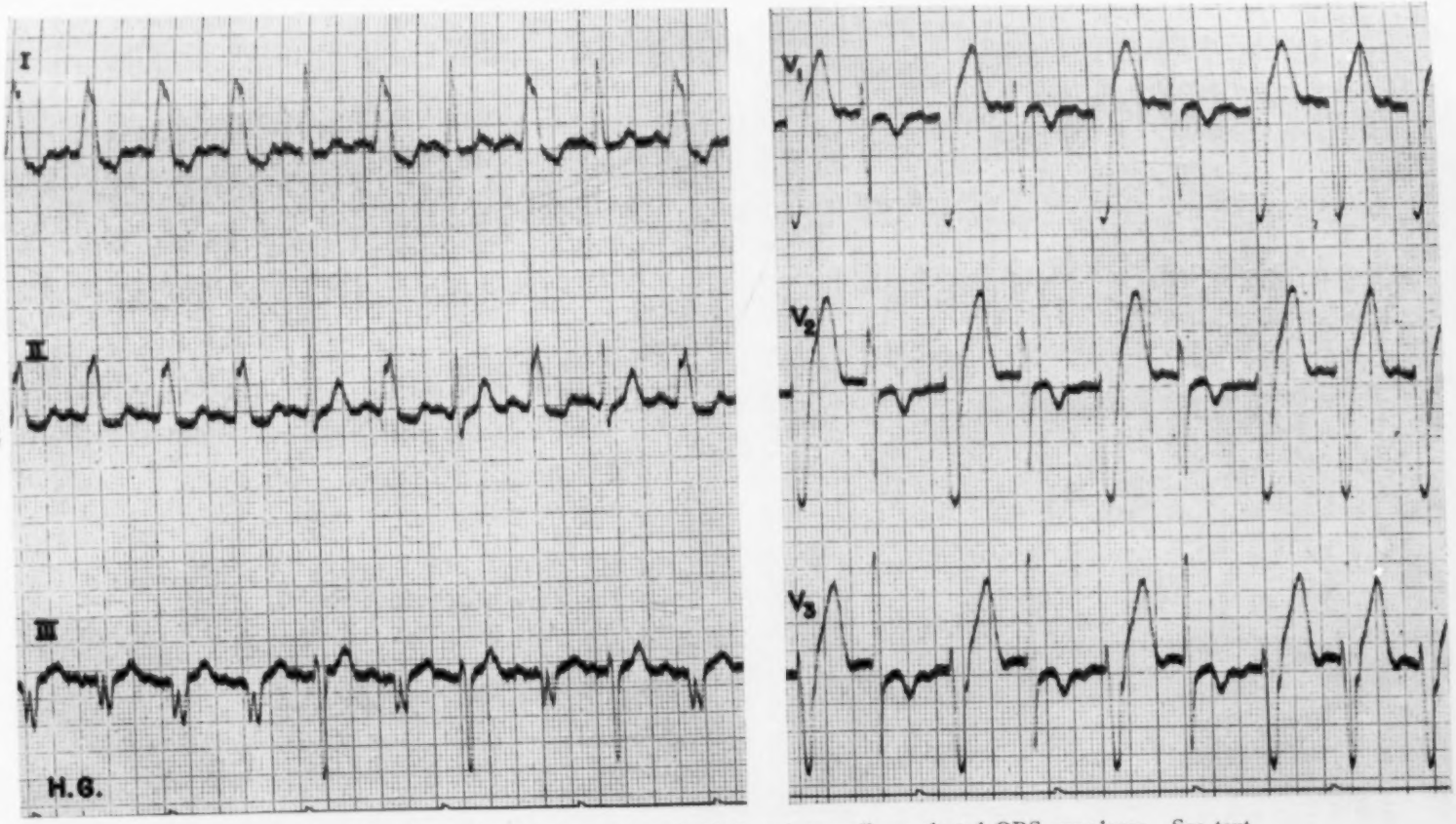

FIG. 6. (Case 7) Alternating left bundle branch block and normally conducted QRS complexes. See text.

premature ventricular complexes followed by compensatory pauses, the latter being followed by left bundle branch block complexes. When the heart rate was slowed sufficiently, normally conducted complexes appeared (figure 7), either following long compensatory pauses or when the R–R interval was 1.30 seconds or more (1.30, 1.48, 1.42 and 1.56 seconds). When either the compensatory pause or the R–R interval was 1.28 seconds or less (.88, 1.08 and 1.28 seconds), no normal complexes appeared. Once normal beats were present, complexes of left bundle branch block re-appeared when the R–R interval decreased to 1.06, 1.14 and 1.08 seconds. Whenever normally conducted complexes appeared, they resembled those seen during normal conduction on previous occasions. Normally conducted QRS complexes were 0.06 second in duration, with deeply inverted T waves in V_1 and V_2 and RS–T segment depression in V_3 and V_6.

Case 8. The patient was a 56 year old white woman with hypertensive heart disease. Her chief complaints were palpitation, dyspnea on exertion, orthopnea, nocturnal dyspnea and occasional edema for seven years. There was no history of angina. The physical examination revealed an obese woman with arteriolar narrowing on funduscopic examination. The heart was enlarged to the anterior axillary line, and a soft apical systolic murmur was present. The blood pressure was 230/120 mm. of Hg. On fluoroscopic examination there was left ventricular hypertrophy with a sclerotic, dilated and tortuous aorta. The laboratory data were as follows: urine, normal; cholesterol, 380 mg. per cent, and urea, 11 mg. per cent. She has been on a low salt diet for two years.

Electrocardiograms: Normal sinus rhythm was present in every record. On May 3, 1948, the electrocardiogram revealed left axis deviation, QRS complexes of 0.08 to 0.09 second, R–R interval of 0.75 second, and a pattern typical of left ventricular hypertrophy. On October 22 the QRS complexes were 0.10 second in duration, with some slurring of the upstroke of the R wave. On September 21 the QRS was 0.11 to 0.12 second and typical of left bundle branch block, with an R–R interval of 0.68 second. Occasionally normally conducted ventricular complexes appeared of 0.08 second duration with an R–R interval of 0.61 second (figure 8A). On March 14, 1950, left bundle branch block was present. Carotid sinus pressure, inhalation of amyl nitrite and inhalation of 100 per cent oxygen for 20 minutes did not produce any change in conduction. Esophageal records were typical of left bundle branch block.[30]

Comment: In these two patients (Cases 7 and 8), left bundle branch block was usually present, but occasionally complexes of normal conduction were recorded. The records of Case 7 were characterized by intermittent left bundle branch block of the 2:1 variety. Only a few reports of similar cases are available in the literature.[33, 42, 43] Normally conducted QRS complexes could be produced in this patient by marked slowing of the heart rate by carotid pressure. The direct effect of the vagus upon the conductive tissue is difficult to evaluate from both the experimental and the clinical results in the literature.[44] The rôle played by the blood calcium in Case 7 is hard to ascertain. In Case 8, the appearance of the normally conducted QRS complexes was seemingly unrelated to heart rate.

Although the electrocardiographic pattern in both of these patients is that of complete left bundle branch block, the bundle branches could still conduct normally for short periods of time. This would indicate that the involved bundle branch is functionally impaired and not completely blocked

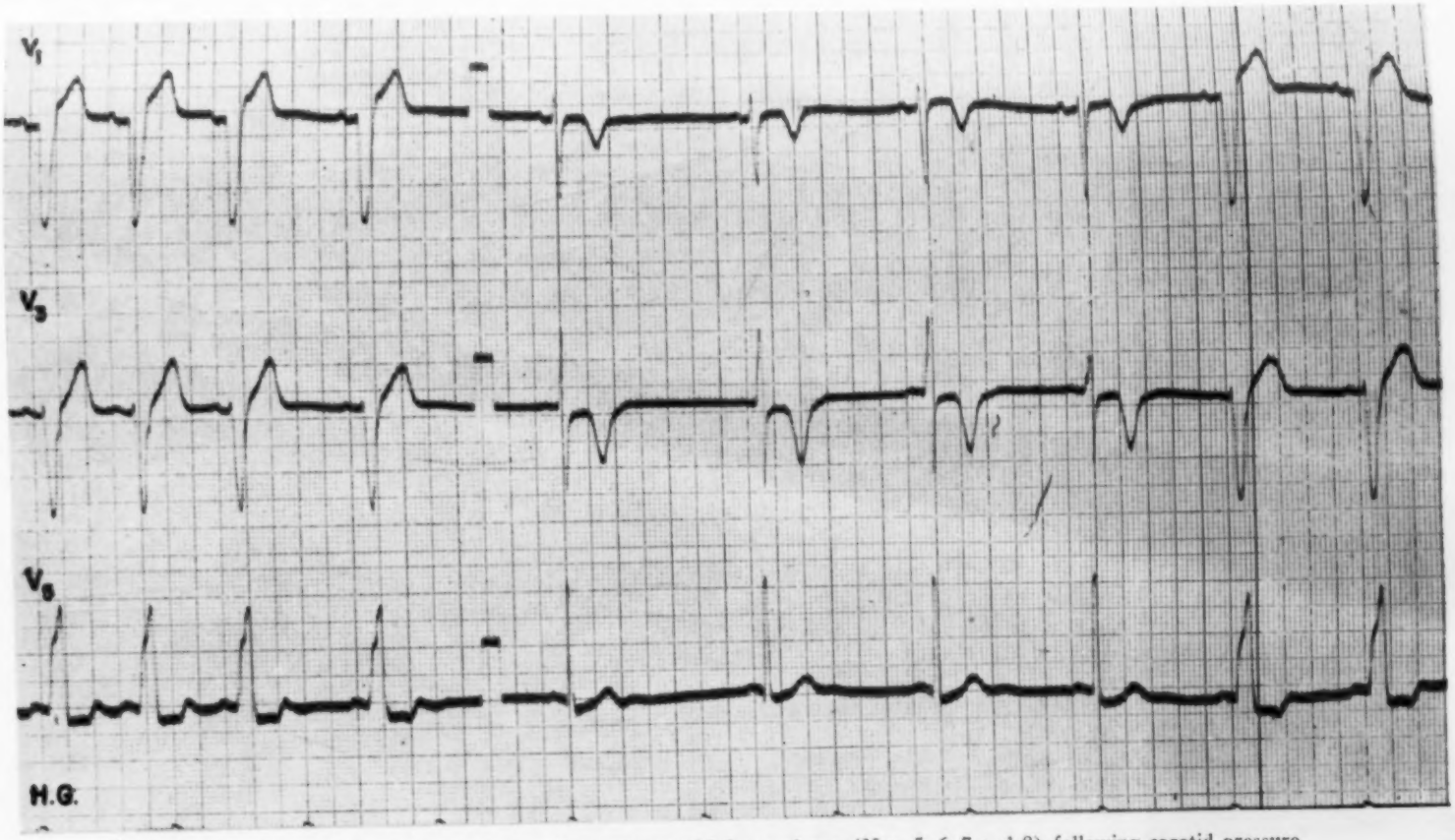

FIG. 7. (Case 7) Appearance of normally conducted QRS complexes (Nos. 5, 6, 7 and 8) following carotid pressure.

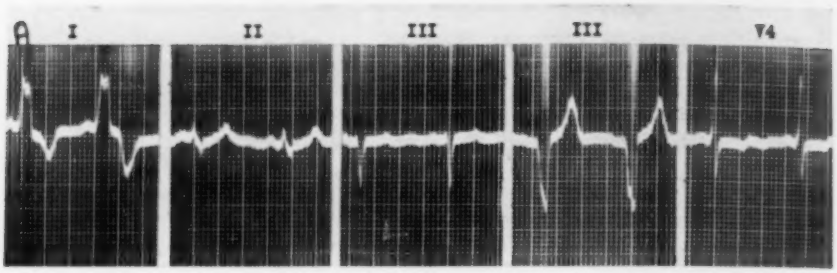

FIG. 8A. (Case 8) Normally conducted QRS complexes in Lead III in the presence of left bundle branch block. See text.

by a localized lesion. Such functional impairment is apparently minimal in effect when the rate is sufficiently slow.

V. *Unstable right bundle branch block of the Wilson type* (QRS complexes of normal duration occurring in the presence of right bundle branch block of the Wilson type):

Case 9. The patient was a 68 year old white woman with a history of hypertension for 19 years, diabetes mellitus for 18 years, and angina pectoris for 14 years. The diabetes has been controlled by diet, with only occasional insulin administration. The angina pectoris has become progressively worse, and the patient has developed increasing shortness of breath. She had infrequent syncopal episodes and palpitations. In 1941, when she was first seen at The Mount Sinai Hospital, examination revealed a grade 1 hypertensive fundus. Her heart was moderately enlarged to the left and the blood pressure was 180/96 mm. of Hg. On June 1, 1950, there was more marked cardiac enlargement to the left, and the blood pressure was 190/100 mm. of Hg. Funduscopic examination revealed moderate diabetic and hypertensive retinopathy. The laboratory data were as follows: urinalysis, zero to 3 plus sugar; cholesterol, 360 mg. per cent, and fasting blood sugar, 98 to 191 mg. per cent.

Electrocardiograms: Regular sinus rhythm was present in every record. On July 23, 1941, the R–R interval was 0.74 second, the QRS complex 0.06 second in duration, and left axis deviation was present. A similar electrocardiogram was recorded on September 22, 1941. On November 7, 1944, the R–R interval was 0.78 second, and the QRS pattern was that of right bundle branch block of the Wilson type. The QRS complex was 0.13 second in duration, and left axis deviation was present. The electrocardiogram on April 4, 1946, was similar to those of July 23 and September 22, 1941. The electrocardiogram on June 24, 1947, was that of right bundle branch block, as on November 7, 1944, with an R–R interval of 0.74 second. On November 1, 1949, right bundle branch block of the Wilson type was present with an R–R interval of 0.72 second. Occasional ventricular premature complexes were present, followed by a compensatory pause (0.85 to 1.13 second) and a normally conducted ventricular complex. The electrocardiogram on June 1, 1950, revealed right bundle branch block with a QRS duration of 0.11 to 0.12 second and occasional premature ventricular complexes (figure 8B). The latter were followed by compensatory pauses (0.91 to 0.96 second in duration) and by normally conducted single complexes or runs of normally conducted ventricular complexes with a QRS duration of 0.06 second. The pattern of the normally conducted ventricular QRS complexes was typical of left ventricular hypertrophy.

Case 10. The patient was a 52 year old white woman with a history of hypertension for three years. Her chief complaints consisted of headache and catching

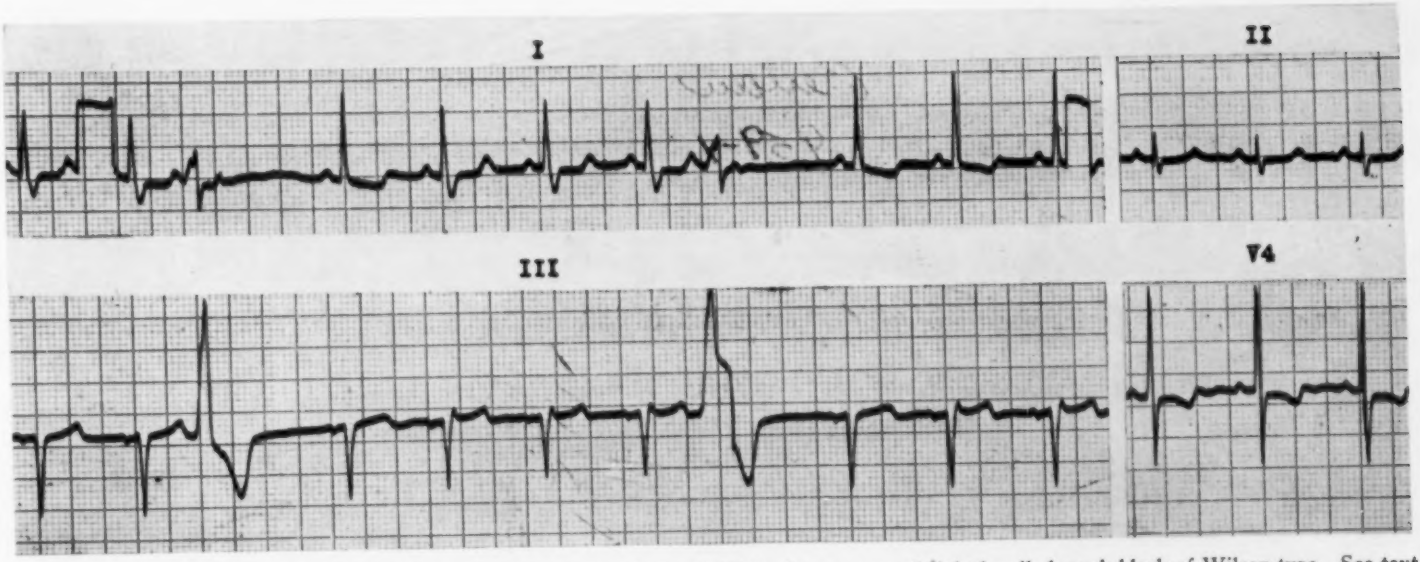

FIG. 8B. (Case 9) Normally conducted QRS complexes in Leads I and III in the presence of right bundle branch block of Wilson type. See text.

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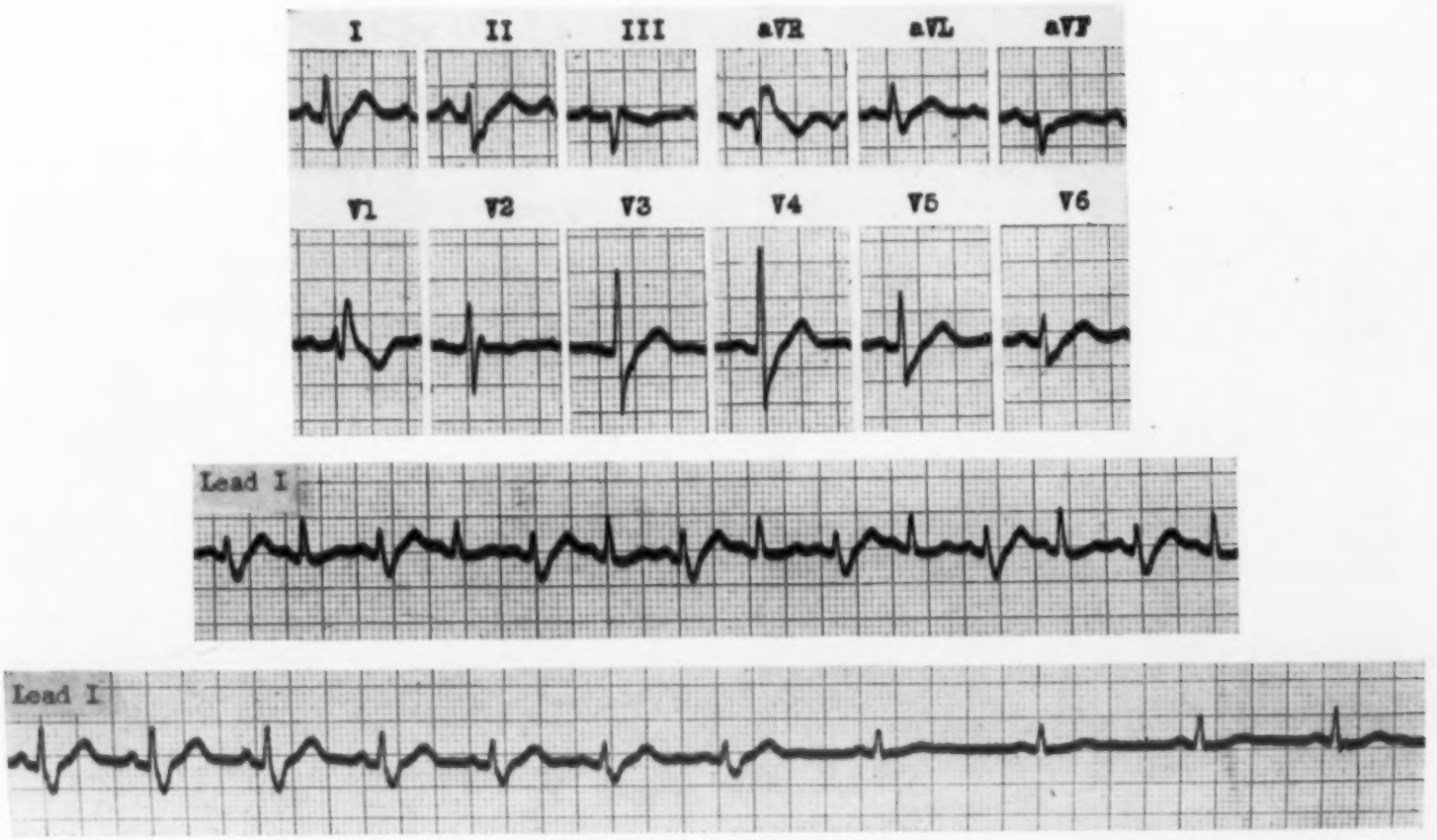

FIG. 9. (Case 10) Unstable right bundle branch block of the Wilson type. Upper record is control electrocardiogram. Lower record, Lead I, reveals alternation and runs of normal ventricular conduction. See text.

precordial pain unrelated to effort. Physical examination revealed an obese woman with slight cardiac enlargement to the left, a soft apical systolic murmur and a blood pressure of 160/102 mm. of Hg.

Electrocardiograms: On July 12, 1949, normal sinus rhythm was present with an R–R interval of 0.54 to 0.56 second. A Wilson type of right bundle branch block was present in the control electrocardiograms, with a QRS duration of 0.11 to 0.12 second (figure 9). Following a single "2-step" exercise test, the patient developed runs of normal ventricular conduction in which the QRS was 0.06 to 0.07 second in duration. Several portions of the electrocardiogram revealed periods of alternation of QRS complexes of normal duration and of right bundle branch block. The R–R interval during the paroxysm was 0.43 second immediately following the exercise. Following two minutes of continuous recording, the pattern reverted to constant right bundle branch block. On July 19 the resting control record revealed alternation of normally conducted QRS complexes and complexes of right bundle branch block with a constant R–R interval of 0.75 second. Several maneuvers were performed, including respiratory and Valsalva's maneuvers, changes in position and exercise. QRS complexes of normal duration frequently appeared, either gradually or abruptly, apparently unrelated to rate. On several occasions transitional complexes were seen as the record reverted from the pattern of right bundle branch block to ventricular complexes of normal duration.

Case 11. The patient was a 22 year old white woman, a nurse, with no history of rheumatic fever, scarlet fever or chorea. Her heart was normal on examination. A routine electrocardiogram three years earlier had shown a right bundle branch block of the Wilson type.

Electrocardiograms: On September 9, 1946, normal sinus rhythm was present with right bundle branch block of the Wilson type. The QRS complexes were 0.12 second in duration (figure 10A). On August 1, 1945, normal sinus rhythm was present with runs of normally conducted ventricular complexes 0.07 to 0.08 second in duration occurring in the presence of right bundle branch block. There was no apparent relationship to rate.

Case 12. The patient was a 64 year old white woman with the chief complaints of abdominal pain and discomfort. The patient had had a cholecystectomy in 1931 and a repair of a ventral hernia in 1932. The cardiac examination on February 20, 1950, revealed soft systolic murmurs at the pulmonic and aortic areas. The heart sounds were distant, and the blood pressure was 160/20 mm. of Hg. The laboratory data were as follows: cholesterol, 400 mg. per cent; urine, normal, and cephalin flocculation, 2 plus.

Electrocardiograms: On February 26, 1948, there was normal sinus rhythm with an R–R interval of 0.78 second. Right bundle branch block of the Wilson type was present with a QRS complex of 0.10 second duration. On February 20, 1950, there was a slight sinus arrhythmia with an R–R interval of 0.82 to 0.92 second. Ventricular complexes of right bundle branch block were intermingled with complexes of normal conduction and duration (0.03 second). Several transitional complexes were noted (figure 10B—continuous record). On March 10, 1950, the following procedures were carried out in an attempt to convert the right bundle branch block into normal ventricular conduction: right and left carotid pressure, exercise, inhalation of amyl nitrite, inhalation of 100 per cent oxygen, respiratory maneuvers, including Valsalva's, and positional changes. Similar procedures were carried out on April 5, 1950. In no instance did QRS complexes of normal conduction occur.

Comment: These four cases are characterized by the presence of right bundle branch block of the Wilson type [45] with occasional appearance of normal QRS complexes. Three of these patients had cardiac involvement

reveals alternation and runs of normal ventricular conduction. See text.

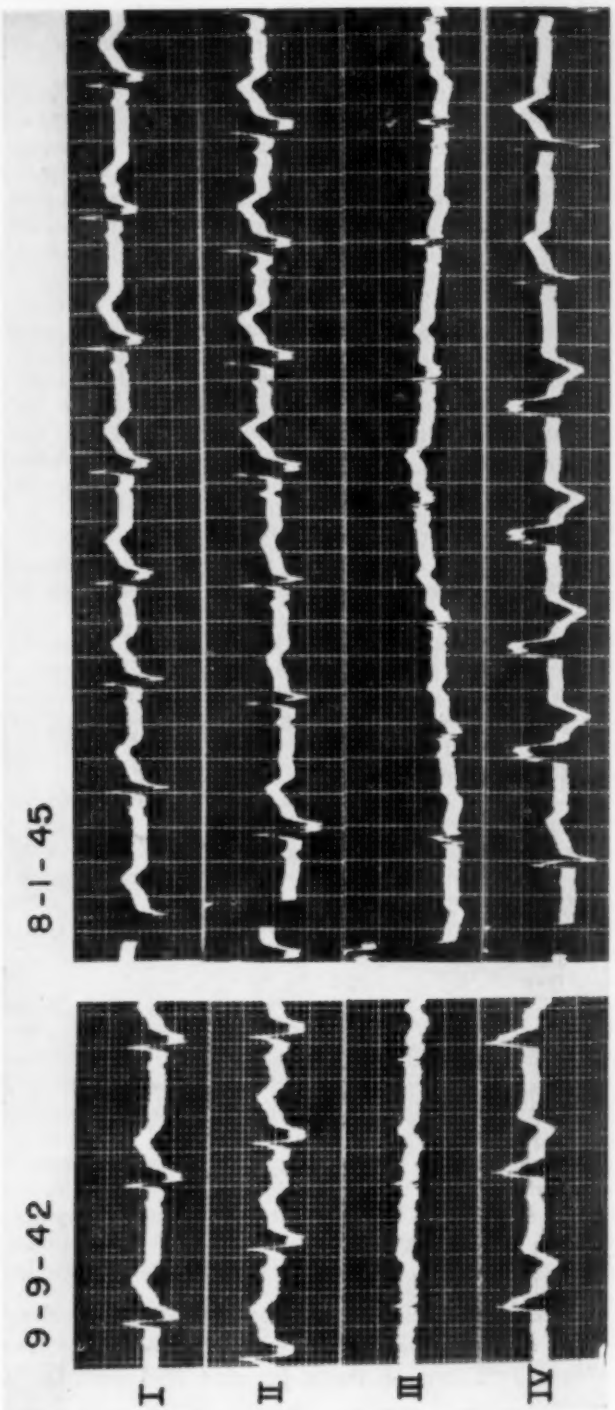

FIG. 10A. (Case 11) Unstable right bundle branch block of the Wilson type. See text.

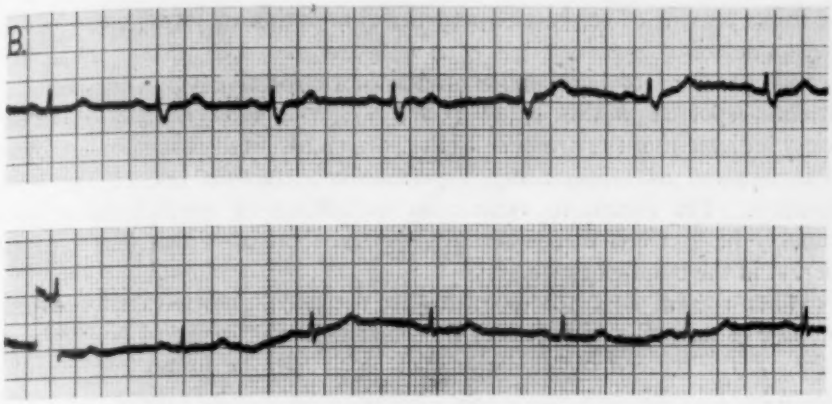

FIG. 10B. (Case 12) Continuous record of normal QRS complexes occurring in the presence of right bundle branch block of the Wilson type. See text.

(Cases 9, 10 and 12) and one had no apparent cardiac disease (Case 11). In one instance (Case 10), the pattern of right bundle branch block could be readily replaced by normal QRS complexes by many maneuvers, including change in position, exercise and respiration, with no apparent relationship to rate. Reports of similar cases have appeared in the literature.[45, 46, 47]

Case 9 is particularly interesting in that the electrocardiograms exhibited right bundle branch block a few years previous to the record revealing normally conducted beats in the presence of right bundle branch block. The last record showed a definite relationship to cardiac rate, the normal complexes appearing after the compensatory pauses following the ventricular premature complexes.

Right bundle branch block of the Wilson type is often associated with no apparent heart disease.[48] In patients with and without heart disease, the appearance of the Wilson type of right bundle branch block in the presence of normal conduction, and vice versa, has been ascribed to change in the tone of the vagus or the autonomic nervous system.[45] The factors permitting normal conduction in these instances await further elucidation.

DISCUSSION

From the data of this study, it is apparent that the pattern of bundle branch block, either right or left, can be present because of many factors. A localized permanent lesion to a bundle branch need not be invoked as the only explanation when such a pattern is seen. Other disturbances, such as tachycardia,[11, 13, 14] pulmonary embolism,[50] positional and respiratory effects,[48] anoxemia,[11, 12] anemia and metabolic derangements,[34, 35, 36, 37, 38] when superimposed on an already diseased heart, may embarrass the conductive ability of specialized tissue. The elimination of these factors may result in

the improvement of conduction and the elimination of intraventricular conduction defects.

The presence of left bundle branch block for five years in one of the patients reported in this study (Case 4), with later normal conduction, would indicate that the presence of the pattern of bundle branch block cannot be interpreted as representing a permanent defect in one of the bundle branches. The return to ventricular complexes of normal duration can probably be ascribed to the removal of some factor which depressed conduction in the bundle branch.

When routine electrocardiograms are recorded, an occasional ventricular complex of normal duration may be found in the presence of bundle branch block, or the pattern of bundle branch block may be found in a record of otherwise normal intraventricular conduction. Such patients should be carefully studied, since the presence of the bundle branch block pattern may be correlated to the factors already indicated, such as anemia (Case 3), tachycardia (Case 5), cardiac failure (Case 6), and infection (Case 2).

Although progressive depression of conduction in a bundle branch appears most infrequently in the literature,[50, 51] five of the present cases (Cases 2, 5, 10, 11 and 12) demonstrated such transitional complexes comparable to the Wenckebach phenomenon in A–V conduction. Though the time period in which such a sequence can be recognized is very short in intraventricular conduction, esophageal leads, as in one of the present cases (Case 5), may vividly demonstrate a progressive impairment of bundle branch conduction. With increasing delay in the left bundle branch, more and more of the septum is activated from the contralateral side so that increasing positivity will be recorded within the left ventricular cavity, as indicated by an R wave of increasing amplitude in the place of the usual QS pattern.[21]

It is difficult to determine accurately the frequency with which the pattern of bundle branch block can be ascribed to a permanent lesion of a bundle branch completely interrupting conduction in this branch. Additional impairment to conduction in an already diseased heart may be sufficient to depress conduction and result in the pattern of bundle branch block. All patients whose electrocardiograms reveal the pattern of bundle branch block should be subjected to several procedures, if their condition permits, in order to ascertain whether normal intraventricular conduction can be demonstrated. Such procedures may include carotid pressure, breathing of 100 per cent oxygen, digitalization if failure is present, and correction of anemia. In this way, it may be possible to determine whether the bundle branch block is due to a permanent unalterable involvement of the conductive system, or whether the conduction defect is essentially functional in character.

Summary

1. Twelve unusual cases of intermittent and transient bundle branch block are presented.

2. In the presence of underlying heart disease, such factors as tachycardia, infection and anemia may impair conduction in the bundle branches.

3. Bundle branch block may be induced in the presence of normal conduction; and normal conduction may be induced in the presence of bundle branch block by altering the cardiac rate.

4. The various aspects of conduction in the bundle branches are discussed.

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LIVER FUNCTION: AN ATTEMPT TO CORRELATE STRUCTURAL CHANGE WITH FUNCTIONAL ABNORMALITY *

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IN recent years some attempt has been made to correlate liver function tests with the histologic changes seen in liver biopsies, most of which have been obtained by the aspiration method.

Sherlock [1] in 1946 compared degrees of liver cell damage with various liver function test abnormalities and noted few significant correlations. Franklin et al.[2] in 1948 reported some association of diffuse liver cell damage and abnormal function tests. In a later work, Popper et al.[3] showed a further quantitative correlation between the severity of damage and the degree of function test abnormality. Kinsell et al.[4] in a small series of cases reported some association between the pathologic picture as a whole and certain liver function tests. Mateer et al.[5] found a general correlation between degree of function change and histologic alteration in cases of cholelithiasis and peptic ulcer. On the other hand, other investigators [6, 7] have found no such correlation in their study of Laennec's cirrhosis.

In this report a statistical comparison is made between the results of each of the function tests and each of 14 demonstrable microscopic alterations seen in liver biopsies obtained from 82 patients. We were particularly interested in attempting to demonstrate whether a single pathologic change is, or is not, associated with a change in one or more liver function tests.

MATERIAL AND METHODS OF STUDY

Clinical Material: A total of 82 patients was studied. These were divided into the following subgroups: 17 cases of stricture of the common bile duct; 32 cases of cholecystitis, of which 26 had cholelithiasis; 13 controls without clinical evidence of liver disease, and a miscellaneous group of 20 patients with abnormal liver function tests. This last group included six cases of congestive splenomegaly, three of Laennec's cirrhosis, two of hemochromatosis, two of liver disease of undetermined type, and one each of pancreatitis, bronchiectasis, hypertensive cardiovascular disease, fatty degeneration of the liver, common duct stone with partial obstruction, cancer of the bladder and cancer of the stomach without visible metastases in each case. On each

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of these patients, liver function tests were done just before operation and a biopsy specimen of the liver was taken at the time of operation.

Liver Function Tests: The 15 function tests used on the great majority of the patients, together with the normal values, are enumerated in table 1. The bromsulphalein test was omitted in cases of clinical obstructive jaundice. In a few cases some tests were not done for technical reasons.

Autopsy Material: Thirty unselected livers from autopsies, excluding those involved by malignancy, were examined. A block was removed from six different sites of the liver, as follows: (1) the gall-bladder bed; (2) the anterior margin of the right lobe, 5 cm. lateral to the gall-bladder bed; (3) the dome of the right lobe; (4) the center of the right lobe; (5) the anterior margin of the left lobe at its mid point, and (6) the caudate lobe. Hematoxylin and eosin were used routinely for staining.

Liver Biopsy Specimen: The biopsy specimen was usually a wedge-shaped piece of liver measuring from 0.5 to 1.0 cm. along an edge and derived from

TABLE I

Liver Function Tests Used in This Study

Test	Normal Value
Thymol turbidity	0–3 units
Thymol flocculation	Not over 1 plus (24 hours)
Cephalin-cholesterol flocculation	Not over 1 plus (48 hours)
Colloidal gold	Not over 1 (24 hours)
Bromsulphalein retention	0–5 per cent in 40 minutes
Urine urobilinogen	Not over 1.0 Ehrlich unit (2–4 p.m. specimen)
Urine bilirubin	0 to 0.25 mg. per cent
Serum bilirubin (prompt reacting)	Not over 0.2 mg. per cent
Total serum bilirubin	Not over 1.0 mg. per cent
Total cholesterol	150–260 mg. per cent
Cholesterol esters	60–75 per cent of total cholesterol
Alkaline phosphatase	Not over 4 Bodansky units
Total serum protein	6–8 gm. per cent
Serum albumin	Not under 4.0 gm. per cent
Serum globulin	Not over 3.0 gm. per cent

the right lobe at the anterior margin and lateral to the gall-bladder bed. A few specimens were taken from the anterior surface of the right lobe or from the left lobe. In 17 cases the biopsy specimens measured from 0.2 to 0.5 cm. in diameter, but in all instances there was sufficient tissue available for histologic study. In every case the specimen was obtained with the liver in full view at the time of laparotomy. The tissue was fixed in Zenker's acetic fluid and was routinely stained with eosin methylene blue. Hematoxylin and eosin, Masson's trichrome green, iron and glycogen stains were used when indicated.

Pathologic Criteria: Each biopsy specimen was examined for the alterations listed below. The changes seen were classified as cytologic or architectural. In the cytologic group were the following: (1) atrophy; (2) regeneration; (3) necrosis; (4) hyaline degeneration; (5) fatty degeneration; (6) polyploidy and mitosis, and (7) proliferation, swelling and/or excessive phagocytosis of the reticuloendothelial cells. In the architectural

group there were (8) periportal inflammation; (9) periportal fibrosis; (10) bile duct increase; (11) bile thrombi; (12) infiltration of liver parenchyma with polymorphonuclear cells; (13) lobular and intralobular zonal change, and (14) vascular alterations. The presence or absence of any of the above was noted. If alterations in cytology or architecture were found, these were rated as mild, moderate or severe, always by a single observer (J. D. F.). The histologic tabulations were done without knowledge of the function tests or clinical diagnosis.

Results

The livers from 30 autopsies, unselected except to exclude those involved with cancer, were studied. Blocks of tissue were taken from six different locations, as described under "Materials and Methods of Study." In 26 of the 30 livers examined, the same histologic picture was found in all six locations. Whatever the process, be it chronic passive congestion, fatty change, zonal necrosis, periportal inflammation, and so forth, the six sections were identical, and one could be substituted for another without altering the microscopic diagnosis. In three of the remaining four cases, the changes present in the six different locations varied quantitatively but not qualitatively. The same microscopic alterations were seen in all six areas, but the severity of these changes varied from site to site. In one case, the biopsy specimen taken from the dome of the right lobe showed marked congestion, while the other five, although histologically similar to each other, did not show this change. Thus, most pathologic processes involving the liver are generally diffuse. Neoplastic involvement and focal necrosis are obvious exceptions. The pathology throughout the liver usually is accurately represented by a single biopsy specimen.

Attempts to correlate various function test changes with histologic abnormalities were carried out. Table 2 shows these relationships. Periportal inflammation and periportal fibrosis were present when there was elevation of total serum bilirubin (above 1.0 mg. per 100 c.c.), of prompt reacting bilirubin (above 0.2 mg. per 100 c.c.), and of alkaline phosphatase (above 4 Bodansky units). Periportal fibrosis was also associated with an elevated urinary bilirubin (above 0.25 mg. per 100 c.c.), but periportal inflammation showed no correlation. There were bile duct increase and bile thrombi when total serum bilirubin, prompt reacting bilirubin and urinary bilirubin were elevated. There was infiltration with polymorphonuclear cells when the urine bilirubin was elevated. All other correlations were not significant.

Although the attempt at correlation was made in the entire group, it was obvious that the subgroups varied pathologically as well as in function test pattern. In the patient control series, histologic changes were found in about half of the cases, although these were minimal in extent. Similarly, the function tests in this group were abnormal in about one-third of the

cases, being slightly beyond the normal range. The common duct stricture cases, on the other hand, all showed histologic alterations and in many the process was extensive and active. In this subgroup the function tests were positive in most of the cases and usually markedly abnormal.

Study of the gall-bladder subgroup showed one or more of the following in almost half of the 32 cases: slight to moderate periportal inflammation, periportal fibrosis, bile duct increase, cell necrosis and infiltration of the parenchyma with polymorphonuclear cells. Fourteen of the 32 cases retained more than 5 per cent bromsulphalein at the end of 40 minutes. Despite these figures, there was no significant correlation between the histology and the dye test. These findings, however, do confirm the work of others [8] in that hepatic injury was found associated with disease of the gall-bladder and that it may be quite extensive.

Binucleated and multinucleated liver cells (polyploidy) were counted in 10 high power fields of each biopsy, or throughout the entire specimen if it

TABLE II

Statistically Significant Correlations

Histologic Alteration	Liver Function Tests			
	Urine Bilirubin	Bilirubin Prompt	Total Bilirubin	Alkaline Phosphatase
Periportal inflammation	No correlation	Positive	Positive	Positive
Periportal fibrosis	Positive	Positive	Positive	Positive
Bile duct increase	Positive	Positive	Positive	No correlation
Bile thrombi	Positive	Positive	Positive	No correlation
Infiltration with polymorphonuclear cells	Positive	No correlation	No correlation	No correlation

Positive correlations refer to an elevated function test and the histologic alteration.

A positive correlation means that an abnormal function test was associated with the above architectural changes 99 per cent or more of the time.

We are indebted to Mr. Louis Rosenblum, of the Polaroid Corporation, for the statistical method and computations.

were small. No significant difference was found in any of the subgroups. The over-all average was 7.3 per high power field. Mitoses were rare, having been seen only five times in the entire study. Assuming that these changes are an index of hepatic regenerative activity, these findings suggest that there is constant and approximately equal repair proceeding in the livers of our controls and subgroups, irrespective of the disease process or its severity in our series.

DISCUSSION

The right and left lobes of the liver are anatomically distinct and perhaps physiologically different in animals.[9-15] The blood in the portal vein derived from the small intestine and right colon tends to remain separated to a large degree from the blood in the same vein derived from the stomach, spleen and

left colon.[9-13, 15] McIndoe and Counseller [16] demonstrated in human beings by injection-corrosion methods that the blood supply and biliary tree of the right and left lobes are sharply demarcated from each other. Stewart [17] and Turnbull,[18] in studying the liver damage of trinitrotoluene poisoning in human beings, found lesions that varied in age and severity in different parts of the liver without reference to lobar localization. Kinney and Ferrebee [19] attempted to show a bilaterality of portal blood supply to the liver by studying the origin of hepatic abscesses.

On the other hand, in our autopsy material, the study of which is detailed above, we found with only one exception that the pathologic change was uniform throughout the liver, although in some cases there was variation in severity of the process. This observation is of fundamental importance in accepting the validity of our biopsy material in liver disease for correlation studies, and we believe that in most instances a single biopsy specimen is representative of the entire organ if cancer is not present.

In the cases studied it was apparent that cytologic pathology, in contrast to architectural pathology of the liver, was lacking or slight. Moreover, cytologic changes, when present, could not be correlated with abnormal function tests. In other words, abnormal results of biochemical function tests were frequently obtained when cytologic changes appeared to be absent, and cytologic changes were occasionally seen when liver function tests were not abnormal.

The lack of cellular change with routine microscopic technic in the presence of abnormal function tests is difficult to explain, particularly in view of the numerous functions attributed to the specialized liver cell. It is certain that numerous enzyme systems, such as phosphatase, lipase and arginase, reside within the liver cell and that protein, carbohydrate and fat metabolism takes place to some extent in this tissue. With ordinary histologic methods these systems are not visible, and consequently it is possible that slight injury to the chemical systems within all of the hepatic cells may occur, impairing the over-all function of the liver so as to result in abnormal function tests and yet not produce cytologic changes visible with the ordinary microscope or routine stains within the individual cells.

It is also known that 75 per cent of the liver can be extirpated and still perform its functions to sustain life. This implies that a large amount of cellular damage may occur but, if the remaining hepatic cells are uninjured and completely normal, there may well be no apparent change in the functional capacity of the liver as determined by present liver function tests.

Abnormal architectural patterns were more readily seen. These included disproportions between stroma and parenchyma, inflammation of the portal regions, zonal necrosis, bile duct increase and the like. Architectural deformity is associated with abnormalities of some of the function tests but not with altered flocculation procedures, bromsulphalein retention, blood cholesterol or blood proteins. Here, also, the methods available for study

of the liver are too gross for satisfactory correlation of morphology and function.

An explanation for the close association between the bilirubin and alkaline phosphatase blood levels and periportal inflammation and fibrosis is speculative. In the case of the phosphatase, the enzyme has been identified in the hepatic cell as well as in many other organs. The source of phosphatase in the blood is unknown, yet in cases of biliary tract obstruction it is elevated. It may be that the enzyme cannot be excreted through the bile ducts distorted by fibrosis and inflammation and is regurgitated into the blood much as bilirubin is. On the other hand, bromsulphalein is presumed to be excreted by the liver cells and carried away by the biliary tract. Yet there was no association in our study between retained bromsulphalein and similar periportal damage.

We are aware that this series does not include some types of liver disease, in particular infectious hepatitis, and that the few correlations seen in our group might not be valid were such cases included.

The absence of correlations as found in this study does not nullify the value of the liver function tests as a whole, since they may measure changes which we cannot yet demonstrate histologically. From a purely clinical standpoint, their general value is well established.

Summary and Conclusions

Most non-neoplastic pathologic processes involving the liver are diffuse and are represented in all lobes. This was established by a study of 30 autopsied livers.

A series of 82 liver biopsies, surgically removed, was studied to correlate structure and function. A battery of liver function tests was done on each case and the results were compared with the microscopic findings of the liver biopsy.

In our cases, an elevated serum bilirubin or an elevated alkaline phosphatase level was associated with periportal inflammation and periportal fibrosis. An elevated serum bilirubin was also associated with a bile duct increase and the presence of bile thrombi. Similarly, elevated urinary bilirubin indicated the presence of bile thrombi, periportal fibrosis, bile duct increase, bile thrombi and infiltration with polymorphonuclear cells.

Using routine histologic methods, morphologic changes in the hepatic cells were slight and could not be correlated with abnormal function tests.

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CASE REPORTS

SEVERE PYELONEPHRITIS DUE TO FRIEDLÄNDER'S BACILLUS TREATED SUCCESSFULLY WITH STREPTOMYCIN *

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Urinary infections caused by Friedländer's bacillus (*Bacillus mucosus capsulatus, Klebsiella pneumoniae*) are not rare. Baehr, Schwartzman and Greenspan [1] reported 50 cases in 1937. Review of the medical literature since that date has disclosed little mention of this disease [25] until the advent of the use of streptomycin. Harris et al.[10] in 1947 reported 21 cases of pyelonephritis treated with streptomycin, five of these due to the Friedländer bacillus. Of these, two were considered cured, one temporarily improved and two unimproved. Kleinman and his associates [16] have also reported therapeutic failures with streptomycin in this disease.

The author considers the following case of interest because of the unusual severity of the infection, the complete bacteriologic and clinical cure, and the use of streptomycin in what is probably unprecedented total dosage for this disease. Other aspects of this case made early, positive diagnosis uncertain. These may be a source of confusion clinically in similar cases.

Case Report

A 20 year old white male was admitted to the medical wards of the Philadelphia General Hospital (service of Frieda Baumann, M.D.) on November 11, 1948. He complained particularly of pain in the back and abdomen, and of passing bloody urine. With the exception of one bout of severe, painless hematuria three years previously, lasting 24 hours, he had experienced no systemic difficulty until three weeks prior to admission. At that time he began to notice constant, dull pain in both costovertebral angles. This pain did not radiate, was more marked on the left and increased on deep inspiration. There was no burning on urination, but shortly after the onset of this pain the urine became "cherry red." He passed a number of minute stones during the 10 days prior to admission and, on several occasions, voided almost "pure blood." Severe night sweats developed, and several days before admission he developed anorexia, nausea and vomiting.

The remainder of the medical history is not particularly pertinent. He recovered without apparent sequelae from scarlet fever at the age of eight, from pneumonia at 10 and from an appendectomy at 14. Intravenous urography prior to admission was reported as revealing renal calcification in both kidneys, with bilateral diminution in renal function. Cystoscopy at that time was reported as showing a "golf-hole" (dilated and fixed) ureteral orifice on the left from which a blood clot protruded.

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Examination on admission revealed a 20 year old white male appearing chronically ill, malnourished, pale and febrile. The initial blood pressure measured 118 mm. Hg systolic and 62 mm. diastolic and remained normal on all future determinations. Large, bilateral subconjunctival hemorrhages were present. Mild pyorrhea with slight bleeding was seen. There were bilateral muscle guarding and tenderness in

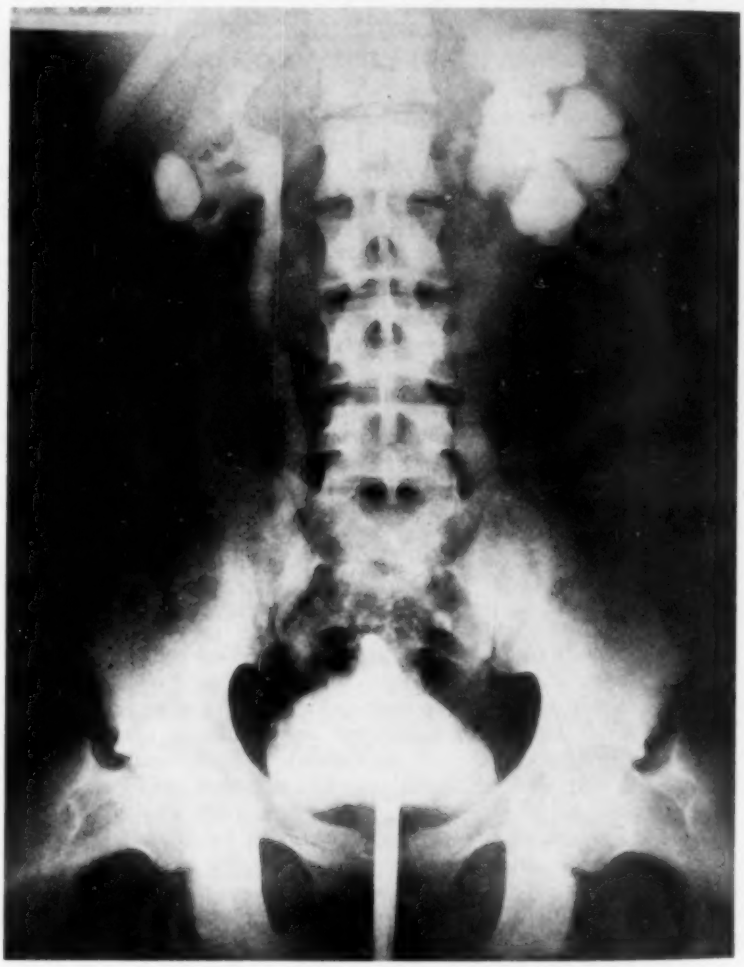

FIG. 1. Retrograde pyelogram taken before streptomycin therapy.

the costovertebral angles, most marked on the left. There was no palpable mass. The examination was otherwise noncontributory.

Routine laboratory studies on admission showed a leukocytosis of 19,000 with 88 per cent polymorphonuclears, a hemoglobin of 13.1 gm. per cent, a blood urea nitrogen of 85 mg. per cent and a grossly cloudy urine containing some pinhead sized stones, 2 plus albumin and a specific gravity of 1.007. Microscopically, the urine proved to be loaded with red cells. A benzidine test for hemoglobin was positive.

The urine culture revealed the Friedländer bacillus in pure, heavy growth. The serologic reaction for syphilis in the blood was negative.

An intravenous urogram revealed extensive, bilateral punctate calcifications in the kidneys which were thought to be parenchymal. There was decreased function of the right kidney. The left kidney showed no sign of function. Cystoscopy revealed moderate inflammation of the bladder. There was purulent drainage from the

FIG. 2. Retrograde pyelogram taken six weeks after completion of streptomycin therapy.

left kidney by ureteral catheter, while the right was grossly clear. Both gave pure culture of the Friedländer bacillus. The indigo carmine function test showed slight impairment on the right. No dye was seen coming from the left kidney at any time. The retrograde pyelogram (figure 1) indicated bilateral hydronephrosis and ureterectasis, with severe distortion of both renal pelves. There were apparent abscess formations and sinus tracts throughout the left kidney and possibly on the right. De-

tailed bacteriologic tests for the tubercle bacillus were continuously negative, but were positive for the Friedländer bacillus, usually in pure culture. Tuberculin skin tests were not done at this time, but two months later were negative in two dilutions (0.00002 mg. and 0.005 mg.) to primary protein derivative.

Shortly after admission the patient began to run a spiking fever. This subsided coincidentally with the administration of 300,000 units of crystalline penicillin every 12 hours for 10 days. The blood urea nitrogen dropped to a level of 45 mg. per cent, where it remained throughout therapy. Urine cultures still showed growth of the Friedländer bacillus 10 days after penicillin therapy was discontinued, and the boy still appeared ill. In view of the continued possibility of renal tuberculosis, the patient was given 1 gm. of streptomycin twice a day, which was to be continued for 60 days as outlined by Nesbit and Bohne.[20] Cutaneous and febrile reactions to streptomycin developed but responded well to oral administration of benadryl. Dihydrostreptomycin was substituted and continued uneventfully for 30 days, being terminated at that time when renal tuberculosis could be definitely ruled out bacteriologically. On the fourteenth day of therapy the urine was known to be sterile, though there is reason to believe that it was sterile before this time.

Six months after the beginning of therapy, the patient remained clinically and bacteriologically cured. Minor vestibular and auditory toxic symptoms completely disappeared. Urine specimens cultured from the bladder and from each kidney separately were sterile. Acid-fast rods were not seen. Review of specimens taken on admission and at intervals thereafter now showed no *Mycobacterium tuberculosis* by culture or guinea pig inoculation. The blood urea nitrogen dropped and remained at a level of 25 mg. per cent.

Recent retrograde pyelogram (figure 2) revealed slight distortion of the calyces compatible with changes due to pyelonephritis. No abscesses were seen, and there was no hydronephrosis. The kidneys were normal in size and had minimal ureterectasis. There was no bladder diverticulum seen at cystoscopy, though it was suggested at a previous cystogram. Both kidneys excreted grossly clear urine, bacteriologically sterile. Indigo carmine dye excretion tests were normal in the right kidney and showed slight impairment in the left.

This patient has gained 15 pounds of body weight since admission to the hospital and has returned to his occupation, light manual labor, without symptoms or signs of recurrence of infection.

Discussion

It is reasonable that streptomycin be considered as therapy of choice for pyelonephritis due to the Friedländer bacillus. Reports on the use of the sulfonamides against this organism have been contradictory. Sulfadiazine has shown a high degree of inhibition against the organism in vitro.[6] Sulfanilamide was found to have no therapeutic effect in mice when injected with 10 M. L. D. of two strains of the Friedländer bacillus.[9] Clinical use in man showed similar results.[5] This experience was substantiated in infection of many of the body systems,[15, 23] though cures of Friedländer infections have been reported with the use of sulfonamides.[18, 19, 22] Penicillin was found entirely ineffective against the Friedländer bacillus in vitro.[13] Clinical value is therefore unlikely, and in the case being reported the use of penicillin did not alter the urinary findings. On the other hand, streptomycin is effective in the experimental animal infected with the Friedländer bacillus,[11] and in pulmonary infections,[12, 14] meningitis [23] and urinary tract infections [10, 16] in man, though the latter met with less than 50 per cent good results.

Early definite diagnosis in this patient was difficult. That urinary tract disease was present was obvious, but certain presenting symptoms and signs were confusing. How were his subconjunctival hemorrhages related to his urinary disease? Were they related to his hematuria? A Rumpel-Leede tourniquet test showed no evidence of capillary fragility. Bleeding and clotting times, as well as the platelet count, were entirely normal. Several negative blood cultures did not confirm bacteremia with embolic phenomena. Acute or chronic glomerulonephritis did not seem a reasonable diagnosis at any time. These questions have therefore remained unanswered. If his disease be confined to the urinary tract, then what was its bacteriologic etiology? The early finding of the Friedländer bacillus in the urine was not diagnostic as being the pathogen, for experience at this hospital has shown that it is a not uncommon urinary invader or bacteriologic contaminant.[4] The Friedländer bacillus has also been observed commonly with other known pathogens in the urinary tract.[1] Several of the urine cultures on this patient substantiated that statement. Nevertheless, this finding of heavy growth of the Friedländer bacillus usually in pure culture and isolated many times from each kidney separately and from the bladder, made it evident that this was the primary infecting organism, provided that one other could be excluded—the *Mycobacterium tuberculosis*.

Punctate, spotty, bilateral renal calcifications, apparently parenchymal, were found on every roentgen study of the abdomen. A dilated and fixed left ureteral orifice seen at cystoscopy was reported by the admitting physician. These findings, together with hematuria, costovertebral angle pain, night sweats and fever, the history of having had an isolated, similar though less severe episode three years previously, and the appearance of a very pale and thin, hyposthenic young male were highly suggestive of renal tuberculosis. Family history of tuberculosis was denied. Chest roentgenograms were normal. A tuberculin skin test was unfortunately not done at this time. Exhaustive search for the appearance of an acid-fast organism was not fruitful. Neither routine smears of bladder urine nor separate smears of the pus from the left kidney or from the urine of the right, or from a 24 hour bladder urine specimen which was centrifuged and concentrated, showed any acid-fast organisms. Conclusive studies by bacteriologic culture or guinea pig inoculation require a minimum period of six weeks' incubation to be valid. It appeared to the author that this patient was dangerously ill and that the safest course to follow was to consider this as renal tuberculosis, with possibly a superimposed Friedländer infection, two such cases having previously been reported,[1] and to begin therapy immediately. It is interesting to note that bilateral renal parenchymal calcification was seen in a young adult female with pyelonephritis due to the Friedländer bacillus in this hospital in 1939.

There are other conditions known to cause renal calcification. Hyperparathyroidism,[3] both primary and secondary, was considered. Blood calcium and phosphorus studies were not diagnostic of such, skull roentgenograms were normal, and there was no palpable mass in the neck. It was pointed out that the type of renal calcification seen in this patient was not typical of that seen in hyperparathyroidism.[17] This diagnosis was therefore discarded—and correctly so, in light of the future clinical course. Vitamin D intoxication is also known to cause renal parenchymal calcification [2] as will sulfonamide intoxication. These were not tenable diagnoses in this patient. Nor did the patient fit the pic-

ture of nephrocalcinosis associated with urinary alkalosis, blood acidosis, isosthenuria and hyperchloremia.[8]

What was the anatomic and physiologic etiology of renal infection in this patient? Did it come to the kidneys by blood stream invasion from another source? The findings of sterile blood cultures, as well as the absence of a possible focus of infection, do not permit definite conclusions to be made on this point, though this seems an unlikely explanation. Was there an obstructive factor in the lower urinary tract? This was found by Baehr and his associates [1] to be the case in 44 out of 50 urinary infections due to the Friedländer bacillus. The findings of bilateral hydronephrosis and ureterectasis by retrograde pyelography pointed suspiciously to the ureterovesical junctions; however, urine was seen to pass through these orifices, there was no obstruction to ureteral catheterization, nor was there any defect seen at cystoscopy at this hospital. That the consideration of obstructive uropathy is not merely academic but rather is important in the maintenance of bacteriologic cure has been well demonstrated.[7, 21] Cystogram did not show ureteral reflux from the bladder. A large, fusiform, posterior defect was outlined in the bladder by cystography. This was interpreted by some as a diverticulum and by others as a normal anatomical variation. Particular care to find this on future cystoscopy did not reveal any visible abnormality. Finally, neurogenic bladder with defective emptying is known to be a factor in the production of bladder diverticula and to cause lower urinary obstructive phenomena.[24] However, following cystography, where approximately 500 c.c. of sodium iodide were injected into the bladder, there was total voluntary emptying of the bladder. Infection without obstruction in the lower urinary passages is known to cause ureterectasis.[4] The question of obstructive uropathy in this case must remain unanswered at this point, though the inability to find it and the absence of hydronephrosis, despite borderline ureterectasis and the continued sterile urine, cast doubt on its existence.

Streptomycin probably has not been given before in the large quantity used in this patient for the treatment of pyelonephritis due to the Friedländer bacillus. The dosage was not calculated here as treatment for this disease. This was considered as one of primary renal tuberculosis for therapeutic purposes. Streptomycin was given intramuscularly, 1 gm. twice daily, for a period of 30 days. Alkali was not given in conjunction with the streptomycin, though it has been demonstrated [10] that it would have been advantageous to do so. Reëvaluation after this 30 day period showed clinical and bacteriologic cure, a negative skin test for tuberculosis, and no growth on the original culture and a negative guinea pig inoculation for the tubercle bacillus. At this time, therefore, renal tuberculosis was definitely ruled out as a possibility, and therapy with streptomycin was terminated. It was not surprising to find symptomatic vertigo as well as demonstrable vestibular and auditory nerve defects as measured by audiometric and caloric studies. This is in accord with others [20] using equivalent total dosage.

What is the prognosis of this patient? That of course can not be answered definitely. Six months following therapy there is no evidence of infection. The retrograde pyelographic studies show a remarkable return toward normal pattern. They do, however, show some evidence of renal damage, as do dye excretion tests—a 50 per cent of normal phenolsulfonphthalein output—minimally elevated blood urea nitrogen levels, and a persistent hyposthenuria. At no time has the

specific gravity of the urine been recorded as greater than 1.010, and there is a continued albuminuria of approximately 3 gm. per day, with excessive casts and red cells in the urine. These are evidences at this time of both tubular and glomerular damage, probably irreversible. What stresses and strains these kidneys can cope with for future years is speculative, but on this therapeutic régime, a remarkable cure has taken place.

It appears reasonable to hypothesize that massive doses of streptomycin may be indicated for the treatment of urinary infections due to the Friedländer bacillus. There are many therapeutic failures on record, all using a much smaller total dosage.[10, 16] It has been demonstrated by Raines [21] that a decrease in sensitivity of these organisms to streptomycin takes place in vitro over a period of a few days. He found this to be true also in infections in man where therapy was stopped for a few days. Unfortunately, sensitivity tests were not done on this patient, so that no statements can be made here on this matter. Perhaps the previous use of streptomycin for the treatment of urinary infections caused by the Friedländer bacillus has been in inadequate total dosage. It is hoped that this paper may stimulate further study along this line.

Summary

1. A case report of severe pyelonephritis due to Friedländer's bacillus treated successfully with streptomycin is presented.

2. Difficulties in finally ruling out renal tuberculosis as an etiologic factor are discussed.

3. The presence of bilateral, renal, parenchymal calcifications are interesting findings in that they are highly suggestive of renal tuberculosis and therefore cause a difficult differential diagnosis.

4. No obstructive uropathy or focus of infection was found to be etiologically related to the renal disease.

5. Streptomycin was given, 60 gm. over a 30 day period. This dosage is probably unprecedented in the therapy of pyelonephritis due to the Friedländer bacillus and may have been responsible for the dramatic therapeutic response.

Addendum

Follow-up examination and studies in May, 1950, approximately 18 months after the illness, show the following:

The patient has worked as a laborer steadily for the last 12 months with no loss of working time due to illness. He feels perfectly well at this time save for slight vertigo occasionally. He has no difficulty walking along a straight line by the heel-to-toe method. There has been a 12 pound gain in weight. One month ago, two small stones were passed by urethra with only mild discomfort. Flat plate of the abdomen still shows the presence of bilateral renal calcinosis. Intravenous urogram now shows fair concentration on the right, while only minimal dye is seen on the left in one hour. There is still the appearance of distortion of the calyces, though the appearance of dye is indicative of improved renal concentrating ability. Blood pressure is 118 mm. Hg systolic and 70 mm. diastolic, hemoglobin 14.6 gm. per cent, blood urea nitrogen 19 and urine specific gravity 1.009, despite a 12-hour fluid restriction prior to the test. There are seen 30 to

50 white cells in the urine per high powered field, occasional hyalin and granular casts. The urine contains 2 plus albumin and is bacteriologically sterile.

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SOLITARY MYOCARDIAL ABSCESS IN SUBACUTE BACTERIAL ENDOCARDITIS *

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On occasion a case of subacute bacterial endocarditis is encountered which presents an unusual feature or combination of features. It is the purpose of this communication to record an instance in which the unique occurrence of myocardial abscess, pericarditis and complete heart block with Morgagni-Adams-Stokes seizures was observed.

Case Report

A 46 year old Italian male barber, with the diagnosis of inactive rheumatic heart disease, had been followed for a long period. He had shown enlargement of the heart, mitral stenosis and insufficiency, aortic stenosis and insufficiency, and normal sinus rhythm. For the two months prior to his final hospitalization, the patient had experienced malaise, headache, fever, vague joint pains, weakness, anorexia and loss of weight.

On admission to the hospital he appeared chronically ill, though well-nourished. Examination of the heart revealed the point of maximal impulse to be in the sixth left intercostal space, 13 cm. from the midsternal line. Thrills were palpable in systole over the aortic area, and in systole and diastole at the apex. Systolic and diastolic murmurs were heard at the apex, the former being transmitted to the axilla. Systolic and diastolic murmurs were present at the aortic area, and the diastolic component was maximal along the left sternal border at the level of the third rib. The cardiac rhythm was regular and the ventricular and pulse rates were 86 per minute. The blood pressure was 120 mm. Hg systolic and 60 mm. diastolic. Neither a gallop rhythm nor a friction rub was heard.

There was no sign of congestive heart failure, the spleen was not palpable and the skin and mucosae were clear. The remainder of the physical examination was noncontributory.

The subsequent course was typically that of a patient with subacute bacterial endocarditis in the pre-penicillin era. The apical rumbling diastolic murmur became inaudible for several days, only to recur. The quality of the other murmurs likewise changed. The temperature spiked between 100° and 105° F., though there was no proportionate tachycardia. Leukocytosis was moderate and anemia developed gradually. The arthralgia subsided shortly after admission. Crops of petechiae appeared in the skin, in the buccal mucosa and in the conjunctivae. Painful nodules were felt in the fingertips. The spleen, however, never became palpable.

Of the four blood cultures which were taken, two were reported positive for alpha prime hemolytic streptococci. Microscopic hematuria was demonstrated, but the urine was otherwise normal. Enlargement of the cardiac silhouette in the long and transverse axes, with accentuation of the right auricular and left ventricular curves, was seen in the teleroentgenogram.

The electrocardiograms taken during the period of attendance at the clinic and during the early portion of the final hospital stay were not beyond normal limits (figure 1A). The electrocardiogram taken on the sixteenth day in the hospital

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exhibited elevation of the S–T segment in Leads I and II (figure 1B). A to and fro pericardial friction rub was heard near the base of the heart. The diagnosis of acute pericarditis was made, but the cause was in doubt.

On the day of death, the patient developed a convulsion which is depicted accurately in this representative excerpt: "The patient was conscious and having periodic respiration with a pulse rate of 60. Suddenly the rate accelerated tremendously and after a few seconds the heart stopped completely. A tonic and clonic convulsion followed with recurrence of the original slow rate after a few seconds and a regaining of consciousness." Following the convulsion, the neurologic ex-

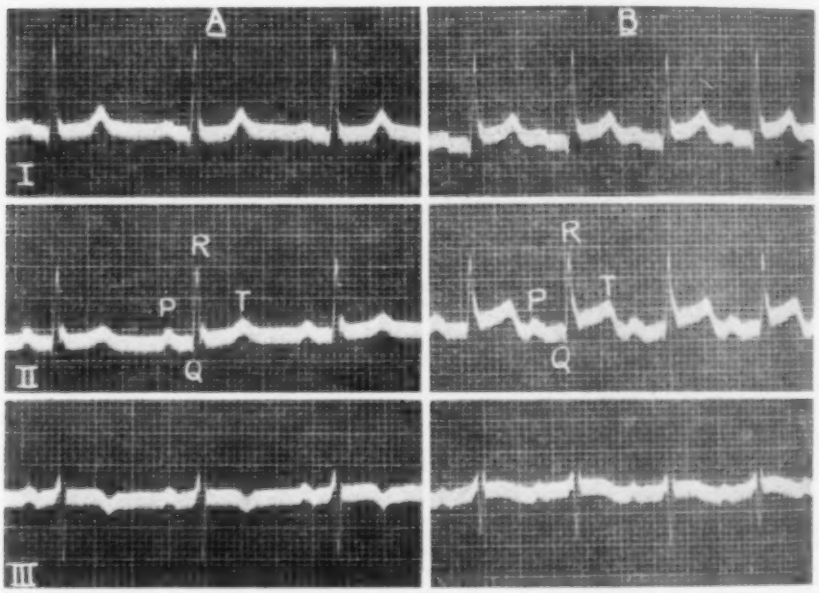

FIG. 1. Electrocardiograms recorded with an interval of 14 days between them before (A) and after (B) the development of acute pericarditis. Both records were made with the string at normal sensitivity. The patient was receiving no medication. In (B) the elevated S–T segments in Leads I and II are to be noted.

amination was normal. An electrocardiogram taken about three and one-half hours after the onset of the convulsion revealed a sinus tachycardia and complete atrioventricular block. The ventricles responded to an idioventricular center, represented in the tracing by aberrant QRS complexes (figure 2).

The blood pressure did not fall, and there was no complaint of precordial pain. The friction rub became more extensive. For these reasons, the diagnosis of coronary occlusion was not favored. It was thought rather that the clinical findings could be accounted for on the basis of sepsis plus suppurative changes in the pericardium and myocardium. Death occurred during one of the syncopal episodes.

At necropsy, the heart weighed 630 gm. The pericardial membranes were pinkish-gray in color and were covered by a shaggy fibrinopurulent exudate (figure 3). The pericardial sac contained 500 c.c. of a dark amber serous fluid.

The mitral valve was thickened and vascularized, and the posterior leaflet was retracted moderately. The attached chordae were somewhat thickened and fused. Running across the free edge of both leaflets was a continuous band of pinpoint-sized, grayish-white verrucae, well covered by endothelium.

A congenitally bicuspid aortic valve was altered to an extreme degree. The posterior commissure between the left and the right cusps was separated approximately 2 mm. The anterior commissure was obliterated and the leaflets were fused completely. The left cusp contained a moderate amount of firm, fibrous tissue and several yellow, soft plaques. On the right aortic cusp there was a fungating mass about 2.5 by 1.5 cm., fragile in its outer portion but moderately firm in its deeper region of attachment. This vegetation involved the entire thickness of the deformed right aortic cusp and had spread to the adjacent portion of the membranous ventricular septum (figure 4).

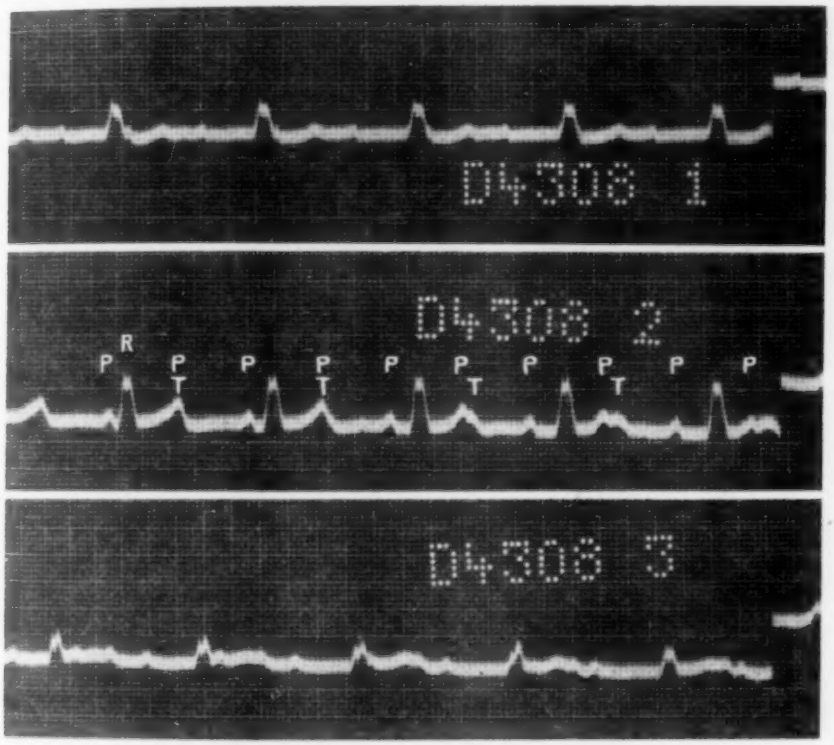

FIG. 2. Electrocardiogram recorded three and one-half hours after the onset of a convulsion. There is complete atrioventricular block. The atria are controlled by the usual sinus mechanism. The ventricles are responding to a center below the bifurcation of the bundle of His, as is evident from the aberrant QRS complex.

Further examination of the interventricular septum revealed it to be the site of a huge abscess which, as a soft grayish-yellow mass, bulged slightly into the right ventricle just below the medial tricuspid leaflet. This projection extended across the septum, past the crista supraventricularis to the conus region beneath the pulmonic ring. At this site it communicated with the pericardial sac through an elevation which previously had been noted externally between the origin of the pulmonary artery and the aorta. No other macroscopic abscess was noted in multiple sections of the heart muscle.

The left ventricular myocardium was hypertrophied, measuring 1.8 cm. at its

thickest portion. The right ventricular myocardium measured 4 mm. The left atrium was enlarged minimally and its endocardium, above the mitral leaflet, was thickened and marked by several pockets. There was, however, no evidence of thrombosis in either auricle, and the pulmonic and tricuspid valves were not remarkable.

FIG. 3. Exterior of the heart at necropsy, displaying fibrinopurulent exudate on the visceral pericardium.

There was no encroachment upon the opening of the coronary arteries. The vessels themselves, except for an occasional small atheromatous plaque, were thin-walled, widely patent and free of emboli.

Microscopic examination of representative areas of the heart disclosed the characteristic changes of subacute bacterial vegetative and ulcerative endocarditis of the aortic valve, of healed (rheumatic type) mitral and aortic valvulitis, of acute sup-

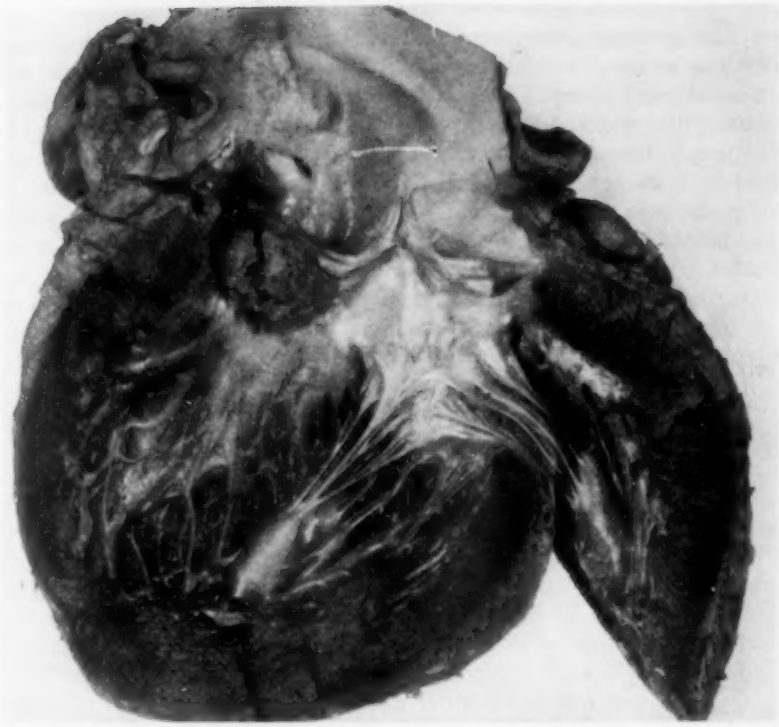

FIG. 4. Interior of the left ventricle, showing the thickened bicuspid aortic valve, the fused commissure between the right and left cusps posteriorly, and the large vegetation (2.5 by 1.5 cm.) on the right cusp extending to the adjacent interventricular septum.

purative and necrotizing myocarditis, fibrinopurulent pericarditis and subacute periaortitis. No stigma of an active rheumatic inflammatory process was observed.

DISCUSSION

The sequence of events in this case is clear. Extension of the aortic endocarditis produced an abscess of the interventricular septum. The abscess bulged into the cavity of the right ventricle and also extended anteriorly to rupture into the pericardial sac. The pericardial perforation was well sealed off. It is not possible to give the exact time of the rupture, though the electrocardiogram revealed findings typical of pericardial inflammation (or, more correctly, of subpericardial myocarditis) at least five days prior to death. The destruction of the atrioventricular node or bundle by the posterior extension of the abscess probably was an agonal event, since both clinical and electrocardiographic evidence of complete heart block was observed only on the day of death.

Myocardial abscess has been found in only 0.2 per cent to 0.56 per cent of the total autopsy material of several large institutions.[1, 2] Such abscesses most frequently have been multiple and usually the result of a wide variety of bacteremias. The extreme rarity of solitary myocardial abscess was commented on by Weiss and Wilkins,[3] who reported two cases of this condition. One case was due to

extension of a pneumococcal mitral valvulitis; the other, to staphylococcal sepsis. In both cases an abscess was found only in the heart, and in both the abscess led to perforation of the heart. Weiss and Wilkins cited seven instances of cardiac rupture by abscess, those of Howitt,[4] Moxon,[5] Haddon,[6] Formad,[7] Rudolf and Moorhouse,[8] Stevenson and Marshall,[9] and McLaglan.[10] The occurrence of cardiac rupture by metastatic abscess in the course of septic infection also was described by Hammer,[11] who found five other examples in the literature. Undoubtedly, the case reported by Chance [12] had an abscess of the heart with rupture, and Krumbhaar and Crowell [13] mentioned three and Davenport [14] two additional cases.

Myocarditis and myocardial abscess are recognized as elements of the structural changes in subacute bacterial endocarditis. In most instances, these elements play little rôle in the course of the disease and in the genesis of its symptoms. Frank necrosis and perforation of a wall of the heart are extremely rare. Osler [15] noted 11 instances of ulceration of the heart leading to perforation of the septum or of a chamber wall. Three of the 11 involved the septum close to the aortic ring. Ulcers at the aortic ring perforated into the left atrium in three instances, into the right atrium in one instance, and into the right ventricle once. In Blumer's [16] summary, small abscesses were recorded only three times. Clawson's [17] series showed 13 instances of abscess in 60 cases. Saphir [2] believed that the commonly found myocardial lesions often were secondary to embolic lesions in minute vessels. Of 44 cases of myocarditis in subacute bacterial endocarditis, he found 32 in the form of abscess in association with pyemia. Flaxman's [1] review brought to light eight cases of myocardial abscess in bacterial endocarditis, though only one was due to infection with *Streptococcus viridans*. In the case caused by *Streptococcus viridans* cited by Barnard and Nariff,[18] several abscesses were found at autopsy. These alterations, symptomless during life, presumably were due to coronary embolism.

The interventricular septum is quite vulnerable to the spread of the bacterial infection, particularly when the aortic valve is affected. Fournier's [19] personally observed case, and six of seven others collected by him from the literature, were examples of septal inflammation and perforation complicating aortic ulcerative endocarditis. Cases reported by Wilson,[20] Stenstrom,[21] Rosenthal [22] and Kidd [23] showed aortic valvulitis and involvement of the adjacent interventricular septum. The clinical diagnosis of perforation of the interventricular septum from extension of an aortic vegetation was confirmed by the postmortem examination in the case described by Levy and Hull.[24]

Occasionally the infection spreads from the right side of the heart through the interventricular septum. Infundibular ulcerative endocarditis with septal perforation was reported by Talamon [25] (Fournier's [19] case 5). Peron's [26] case of postpuerperal ulcerative endocarditis spread from the tricuspid leaflet to perforate the septum. The amazing case reported by Fisher and Longcope [27] affected primarily the pulmonary valve and artery, with transseptal extension. *Streptococcus viridans* tricuspid valvulitis, with erosion and perforation of the membranous interventricular septum, was observed once by Nickson and Brown.[28]

Involvement of the interventricular septum, whether by simple inflammatory reaction or by abscess, may disturb the cardiac rhythm. Disorders of cardiac

rhythm are uncommon in bacterial endocarditis, but the presence of an abscess or an active inflammatory process in the septum may compromise the atrioventricular node or bundle and its major branches so that atrioventricular or intraventricular conduction are affected. This impairment may range from simple prolongation of the PR and QRS intervals to complete heart block. One of the patients of Rothschild et al.[29] had septal extension producing left bundle branch block. Stenstrom's [21] patient had a prolonged PR interval, dropped beats and atrioventricular dissociation; sudden death occurred during a paroxysm. Cases 4 and 5 of Rosenthal [22] had evidence of septal involvement at autopsy. In the former case no electrocardiogram was obtained, but the slow ventricular rate (30 to 40 per minute) suggested heart block. Segal's [30] study of 192 cases of bacterial endocarditis, with electrocardiograms in 67 cases, disclosed nine cases of heart block, two of prolonged QRS interval and one of left bundle branch block.

It is significant that interventricular septal participation in the production of the conduction defects is much more likely when the aortic valve is the site of the endocarditis. This is a striking finding in the analysis made by Segal,[30] who demonstrated that the involvement of the aortic valve alone or in combination was much higher in the group with rhythmic disorders (especially heart block) than in the group with normal rhythm. Disturbances in conduction time with aortic vegetative endocarditis were also mentioned in cases cited by Rothschild et al.,[29] de la Chapelle and Graef [31] and Winternitz.[32] Seven of the eight protocols given in Fournier's [19] thesis indicated aortic disease, and although this study long antedated the introduction of the electrocardiographic method, the syncopal episode which occurred in his patient shortly before death most probably was the onset of complete heart block. Similarly, the cases of Wilson,[20] Stenstrom [21] and Rosenthal,[22] with conduction disorders, had aortic endocarditis.

The closest resemblance to our case is found in the reports by Wilson [20] and Kidd.[28] Wilson's second patient, a 50 year old male, bore the clinical diagnosis of subacute bacterial endocarditis. The electrocardiogram originally showed delayed atrioventricular and defective intraventricular conduction and left ventricular preponderance. Syncopal seizures developed, and the electrocardiogram revealed complete heart block with defective intraventricular conduction. Death was sudden, and at autopsy the aortic valve was found to be the site of a vegetative endocarditis. A necrotic cavity extended through the interventricular septum. The third of Wilson's cases was a 43 year old white male who was found at necropsy to have *Streptococcus viridans* aortic endocarditis, with septal erosion into the right auricle. Shortly before the death of this patient, his pulse rate had dropped from its usual 120 beats per minute to about 50 and, though an electrocardiogram was not obtained, it was believed that acute heart block had developed.

Kidd's patient was an 18 year old boy, ill of rheumatic heart disease and subacute bacterial endocarditis. No electrocardiogram is included in the protocol, but the patient complained several times during his illness that his heart "stopped." At autopsy, after an unexpected instantaneous death, a large mycotic aneurysm was found at the site of the atrioventricular node, eroding from the left ventricle through to the right atrium, and almost perforating the interventricular septum. A footnote to the paper included another instance in which the

electrocardiogram demonstrated a prolonged PR interval and then complete heart block, and the necropsy revealed subacute bacterial endocarditis of the aortic valve with ulceration through the septum into the right atrium.

The occurrence of pericarditis with subacute bacterial endocarditis is unusual, and most of the reviews of the latter disease emphasize this point.[15, 16, 33, 34, 35, 36] The pericardial reaction may be due to the bacterial endocarditis alone. This is particularly true when the infection complicates congenital heart disease, calcareous aortic valve disease and similar noninflammatory lesions. The infection may reach the pericardium in several ways. The aortic wall may be eroded by a lesion in the sinus of Valsalva. A mycotic aneurysm of a major coronary artery may rupture into the pericardial sac. A suppurative focus in the myocardium (the result of minor coronary embolism or direct extension of the valve infection) may perforate into the pericardium.

When subacute bacterial endocarditis complicates rheumatic heart disease, the pericarditis may be the result solely of the rheumatic process and be characterized by either obliterative or exudative reactions, or both. The possibility exists here for a third group of cases, in which the pericardial lesions are due in part to the rheumatic disease and in part to bacterial endocarditis.

In the case reported above, though the infective lesion was imposed on a heart deformed by rheumatic fever, examination of many sections of the organ disclosed no evidence of active rheumatic inflammation. This, then, represents an instance of pericarditis due to subacute bacterial endocarditis alone. Beck [37] has given the protocols of five patients with pericarditis, in four of whom this occurred during *Streptococcus viridans* endocarditis, and presumably also in the fifth. The underlying heart disease was of the congenital or degenerative type, and in all five the aortic valves were affected. An interesting sidelight on this problem is the case report by Hargrove [38] of a 16 year old boy who developed an acute pericardial effusion after an upper respiratory infection. The *Streptococcus viridans* was cultured from the blood and pericardial fluid. The patient recovered after treatment.

Summary

The unusual occurrence of a solitary myocardial abscess, suppurative pericarditis and complete heart block with Morgagni-Adams-Stokes seizures during the course of classical *Streptococcus viridans* endocarditis has been presented. Involvement of the interventricular septum with terminal complete block of atrioventricular conduction was secondary to a vegetative process on a congenitally bicuspid aortic valve which displayed evidence of healed rheumatic disease. Pericarditis, a rare complication of subacute bacterial endocarditis, resulted from direct extension of the abscess to the pericardium.

Addendum

Since this manuscript was submitted for publication, another instance of complete heart block occurring during the course of acute bacterial endocarditis has been reported by Frankel (Ohio State M. J. **45**: 1176, 1949).

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TETANUS, A SEVERE CASE WITH RECOVERY *

By Fletcher B. Taylor, M.D., F.A.C.P., Robert G. Parsons, M.D., *Oakland, California,* and Howard E. Hansen, M.D., *San Francisco, California*

Case Report

On April 8, 1948, a 17 year old boy scratched the skin on the medial side of his ankle while running a hurdle race. The small wound bled very little and was nearly healed three days later. On April 12 he struck the abrasion with the spike of his track shoe and reopened it. On that day he began to have diffuse soreness in the low back. During the next three days, the soreness in the back became more severe and more general. With rapid increase in this soreness and in muscle tension, he was hardly able to move on April 15, seven days after the original injury. He was in extreme pain and very rigid, could not open his jaws more than one-fourth of an inch and could not urinate. He was brought to the hospital in a state of marked general rigidity and opisthotonos.

Physical examination revealed the signs mentioned above, as well as risus sardonicus. The pupils were small and equal and reacted to light and on accommodation for distance. There were a striking increase in muscle tone and a complete inability to relax any of the muscle groups. The pulse rate was 76 per minute, the blood pressure 126 mm. Hg systolic and 70 mm. diastolic, per minute. His mind was clear and he made remarkable efforts to coöperate during examination and in the treatment which followed. The reflexes were hyperactive and may have been slightly more active on the left side than on the right. Examinations were kept at a

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From the Isolation Department of Highland Alameda County Hospital, Oakland, California.

minimum because of prompt increase in muscle tone with any stimulation. The Babinski was negative.

A tentative diagnosis of tetanus was made on the basis of the history and physical findings. A smear of the small wound on the left ankle revealed no organisms resembling tetanus bacilli or spores. Five thousand units of anti-tetanus serum were given at that site. At the same time, 100,000 units were given intravenously and 15,000 intramuscularly. Subsequent observations included the following: Spinal fluid pressure was 330 mm. Hg; cell count was 1 leukocyte and 7 erythrocytes per cu. mm. Catheterized urine showed a few granular casts and a few leukocytes per high dry field, and was otherwise normal. Blood Wassermann reaction was negative.

Encephalitis and poliomyelitis were considered but excluded in the light of the clinical picture and the spinal fluid findings.

Treatment was carried forward with the several parallel measures which are shown in the accompanying chart. The object of treatment was to neutralize any unfixed toxin and to prevent spasms through the use of curare and barbiturates.

TABLE I

Daily Totals

Hosp. Day	Date	Sodium Amytal	T.A.T.	Intocostrin 20 mg./c.c.	d-Tubocurarine in Oil and Wax	Other
1	4–15–48	4 gr.	100,000 U IV 15,000 IM 5,000 Loc.		30 mg. IM	
2	4–16–48	45	100,000 U IV		30	Duracillin 600,000 U
3	4–17–48	45	80,000 U IM			Duracillin 600,000 U
4	4–18–48	45	40,000 U			Duracillin 600,000 U
5	4–19–48	45		120 U IV		Duracillin 600,000 U
6	4–20–48	39	40,000		30	Duracillin 600,000 U
7	4–21–48	54	40,000			Duracillin 600,000 U
8	4–22–48	45	40,000			Duracillin 600,000 U
9	4–23–48	54	40,000			Duracillin 600,000 U
10	4–24–48	63		20 IM	30	Duracillin 600,000 U
11	4–25–48	54				Duracillin 600,000 U
12	4–26–48	54		20	30	Duracillin 600,000 U
13	4–27–48	52		40		Duracillin 600,000 U
14	4–28–48	42		120	30	Duracillin 600,000 U
15	4–29–48	33		120		Duracillin 600,000 U
16	4–30–48	36		120	30	Duracillin 600,000 U
17	5–1–48	30		120		
18	5–2–48	33		120		
19	5–3–48	27		120		
20	5–4–48	24		120	30	

TABLE I—*Continued*

Hosp. Day	Date	Sodium Amytal	T.A.T.	Intocostrin 20 mg./c.c.	d-Tubocurarine in Oil and Wax	Other
21	5–5–48	21		110		
22	5–6–48	6		40	30	
23	5–7–48	6		40		
24	5–8–48	6			30	
25	5–9–48	3				Dicumarol 600 mg.
26	5–10–48	15			30	Duracillin 600,000 U
27	5–11–48	15		100		Duracillin 600,000 U
28	5–12–48	12		100	30	Duracillin 600,000 U
29	5–13–48	9		100		Dicumarol 100 mg.
30	5–14–48	9		100	30	
31	5–15–48	6		40		
32	5–16–48			40	30	Dicumarol 100 mg.
33	5–17–48					Dicumarol 100 mg.
34	5–18–48					
35	5–19–48					
36	5–20–48					
37	5–21–48					
38	5–22–48					
39	5–23–48					
40	5–24–48					
Totals		908 gr.	540,000 U	1,710 U	420 mg.	Duracillin 12,000,000 U Dicumarol 900 mg.

A Levine tube was passed through the nose into the stomach and kept in place for several days because the patient choked when being fed. A Foley catheter was inserted into the bladder. These indwelling tubes decreased the number of disturbing stimuli, thereby reducing the number of spasms. Duracillin was used prophylactically to prevent infectious complications around the tubes and in the lungs.

Curare was used in aqueous solution and in wax base,* and barbiturates were used liberally to minimize spastic episodes from various unavoidable stimuli.

The generalized muscle spasm continued, but a gradual decrease was apparent as a result of the combined measures. We were fearful of respiratory paralysis by overdose of curare and therefore kept an oxygen supply on hand. Our caution may have been too great, as there were some spasms which stopped the respiratory movements for considerable periods of time, and in retrospect we believe that more generous use of the curare may have been warranted.

On the fifth day of treatment the patient could urinate and the catheter was removed. On the sixth day he was able to swallow liquids, and the Levine tube was removed. There followed several days of moderate improvement, but with continuation of marked rigidity of the muscles and with occasional spasm.

Redness and swelling of the right forearm and enlargement of the axillary lymph nodes were noted on the fourteenth day. This was considered to be a thrombophlebitis. It resolved slowly without specific treatment.

From the fifteenth day to about the twenty-second day he had a moderately severe

* Tubocurarine, Squibb.

generalized urticaria, which was thought to be serum sickness. Benadryl in 100 mg. doses was helpful in relieving the itching. Meanwhile there had been marked relaxation of the muscles and cessation of spasms.

On the sixteenth day the curare in wax was discontinued, but four days later, despite the steady use of aqueous curare, muscle tone had increased and spasm recurred. The curare in wax was resumed and within 24 hours there was striking improvement.

This phase of improvement lasted until the twenty-fifth day, when he developed severe pain in the left calf. There was tenderness along the course of the saphenous vein, the left calf was tender, the superficial veins of the left foot were distended, and Homan's sign was positive. The femoral vein was opened under local anesthesia, a clot removed as completely as possible and ligation done. The occurrence of phlebothrombosis and ligation of the vein appeared to precipitate a recurrence of spasms and increased muscle tone. Continuation of the antispasmodic measures again was followed by a favorable trend, and on the thirty-first day these measures were successfully discontinued. Since this time the patient has continued to be well and has resumed scholastic activities, including moderate athletics. The left leg is larger than the right, apparently more because of dilated venous channels than because of edema.

During the 32 days of antispasmodic treatment the average amount of curare in wax available daily was 13 mg., and the average interval between doses was 2.4 days. Four-day intervals were found to be too long when tried early in the illness, and a two-day interval was found to be safe and more effectual.

Aqueous curare was given as indicated symptomatically during the 20-day period shown on the chart. It was used at intervals of a few hours, as determined by the muscle tone and the tetanic episodes. One hundred twenty units (18 mg.) per day were used in this manner.

The sodium amytal was given by nasostomach tube while in place, and by capsule after the tube was removed. The average available amount during the tetanic period was 30 gr. per day. The maximum in 24 hours was 63 gr.

Summary and Conclusions

The history, physical findings and treatment of a severe case of tetanus are outlined.

Treatment consisted of tetanus antitoxin, aqueous curare, curare in wax, and amytal.

The occurrence of phlebothrombosis suggests that anticoagulant therapy may be indicated in such cases in the future.

PSEUDOMONAS AERUGINOSA MENINGITIS FOLLOWING SPINAL ANESTHESIA: REPORT OF TWO SUCCESSFULLY TREATED CASES*

By Bernard H. Pastor, M.D., William I. Gefter, M.D., F.A.C.P., and Samuel Baer, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

Meningitis due to *Pseudomonas aeruginosa* (*B. pyocyaneus*) is rare. At the Philadelphia General Hospital during the 10 year period 1939 to 1949, only

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one meningeal infection with this organism (in association with a brain abscess) has been observed. The organism has been reported in spinal fluid culture as a contaminant on four other occasions. During the same period, there were 429 cases of meningococcic meningitis, 215 cases of pneumococcic meningitis, 26 cases of *Hemophilus influenzae* meningitis and 133 acute meningitides of other etiology.

Stanley,[1] in his extensive review of *Bacillus pyocyaneus* infections, cited 41 cases of primary *B. pyocyaneus* meningitis in the literature prior to 1947. Fourteen cases followed diagnostic lumbar puncture, 13 resulted from traumatic penetration of the meninges, 10 followed spinal anesthesia, two followed pneumoencephalography, one resulted from infection of a spina bifida, and one resulted from intraspinal administration of tetanus antitoxin. The mortality in this group, who were treated with spinal drainage and sulfonamides, was 55 per cent. In an additional group of 29 cases, *B. pyocyaneus* infection of the meninges occurred secondary to a focus elsewhere, or as part of a septicemia. This group had an even greater mortality (86 per cent).

Harris and her associates [2] observed four cases of *B. pyocyaneus* meningitis which developed during intrathecal penicillin therapy for pneumococcic meningitis. The source of infection was traced to contamination of penicillin solutions during their preparation. Two of the four patients died.

Treatment of this infection with sulfonamides [1] or with penicillin [2] is generally unsatisfactory. Cairns and his coworkers [3] used intrathecal streptomycin in three patients acutely ill with *Ps. aeruginosa* meningitis following unsuccessful treatment with penicillin and sulfonamides. All of the patients died. Merwarth and his associates [4] successfully treated a case of Pseudomonas meningitis with streptomycin. They used 1 gm. per day intramuscularly for 15 days, and 50 to 100 mg. per day concurrently by the intrathecal route. A severe neurotoxic reaction to the drug developed three weeks later. Among 27 cases of meningitis due to gram-negative bacilli treated with streptomycin by Paine and his associates [5] were three cases of *Ps. aeruginosa* infection; two, in infants, resulted from infection of a congenital meningocele, and one, in an adult, followed diagnostic lumbar puncture. Two of the three patients had been treated with penicillin for two and four days, respectively, and the third with penicillin and sulfonamides for three days, without response. The adult and one infant recovered following combined intrathecal and intramuscular streptomycin therapy. The dosage used in the infants was 200 mg. per day intramuscularly for 23 and 30 days, respectively, and intrathecal doses ranging from 10 to 50 mg. daily for the same period. The adult received 4 gm. per day intramuscularly for seven days, and 50 mg. per day intrathecally for eight days. Weinstein and Perrin [6] treated three cases of primary *B. pyocyaneus* meningitis successfully with intrathecal and intramuscular streptomycin combined with a sulfonamide. In two of their patients the meningeal infection relapsed one and four times, respectively, when treatment was stopped. Deafness developed in all three, and one showed severe labyrinthine disturbance. In the light of present experience, the toxic reactions were probably related to the large doses and prolonged use of streptomycin. The patients received 100 mg. daily for a total of 8.1, 2.9, and 1.8 gm. of streptomycin intrathecally, and 4.0 gm. daily for a total of 36.5 gm., 83 gm., and 227 gm. intramuscularly, respectively. To date there are 10 reported cases

treated with streptomycin, with six recoveries. Serious toxic reactions were observed in four of those surviving.

We have recently observed and treated successfully two cases of *Pseudomonas aeruginosa* meningitis which followed spinal anesthesia.

Case Reports

Case 1. A 21 year old negro woman was admitted to a hospital on February 22, 1949, where an appendectomy was performed under spinal anesthesia. Postoperatively the patient complained of frontal headaches, which were relieved by medication. The day following her discharge on March 2, the headache recurred and radiated to the back of the head and neck. Fever and night sweats developed. The headache became intense and was accompanied by vertigo, nausea and vomiting. On March 8 she was admitted to the Philadelphia General Hospital with severe headache and a temperature of 104.2° F. Examination disclosed nuchal rigidity, a positive Kernig sign and hyperactive deep reflexes. There were no other remarkable physical findings except for a recent, well-healed right rectus incision.

On admission, lumbar puncture revealed cloudy spinal fluid under a pressure of 200 mm. of water which contained 1,695 white blood cells per cu. mm., all polymorphonuclear leukocytes. The white blood count was 2,750 per cu. mm., with 81 per cent neutrophils, 16 per cent lymphocytes, 1 per cent eosinophils and 1 per cent basophils. The following day the white blood count was 15,500 per cu. mm., with a similar differential count. The hemoglobin was 10.8 gm., blood urea nitrogen 24 mg. per cent, blood sugar 70 mg. per cent, urine straw colored, alkaline, specific gravity 1.010, trace of albumin, 8 to 12 white blood cells and 1 to 2 red blood cells per high power field. Serologic test for syphilis was negative.

Treatment was instituted with crystalline penicillin in dosage of 100,000 units every three hours intramuscularly, after an initial intrathecal dose of 15,000 units and an intravenous dose of 500,000 units. Three grams of sulfadiazine were given initially, followed by 1 gm. every four hours for two days.

On March 9, gram-negative bacilli were identified in the smears of the original spinal fluid, and *Ps. aeruginosa* was cultured from separate spinal fluid specimens obtained on March 8 and March 10. The organism was resistant to streptomycin in vitro in concentrations of 2.5 units per ml., and sensitive to 5 units per ml. Dihydrostreptomycin in doses of 2 gm. per day intramuscularly was given from March 10 to March 23. A 50 mg. dose of streptomycin was administered intrathecally every day from March 11 to March 14. On March 10 the dose of penicillin was reduced to 50,000 units every three hours and was continued until March 16.

The temperature fell by lysis and there was gradual clinical improvement. On March 14 the spinal fluid cell count had fallen to 528 per cu. mm., with 12 per cent polymorphonuclears and 88 per cent lymphocytes. She became ambulatory and was afebrile for 12 days. On March 27 she was noted to have malaise and a temperature of 101° F. The following two days she was asymptomatic and afebrile. On March 30 her temperature rose to 104° F. Severe headache and nuchal rigidity returned and the patient was again acutely ill. A spinal fluid examination revealed an increase to 2,880 cells per cu. mm., 82 per cent polymorphonuclears, 18 per cent lymphocytes. Culture of the spinal fluid, however, was negative. Roentgenograms of the sinuses and mastoids were normal.

Dihydrostreptomycin in doses of 2 gm. per day was resumed on March 30, and intrathecal streptomycin in doses of 50 mg. was given daily from March 30 to April 4. Again there was prompt clinical response. The drug was continued until April 12 and the patient remained symptom-free. The spinal fluid pleocytosis subsided

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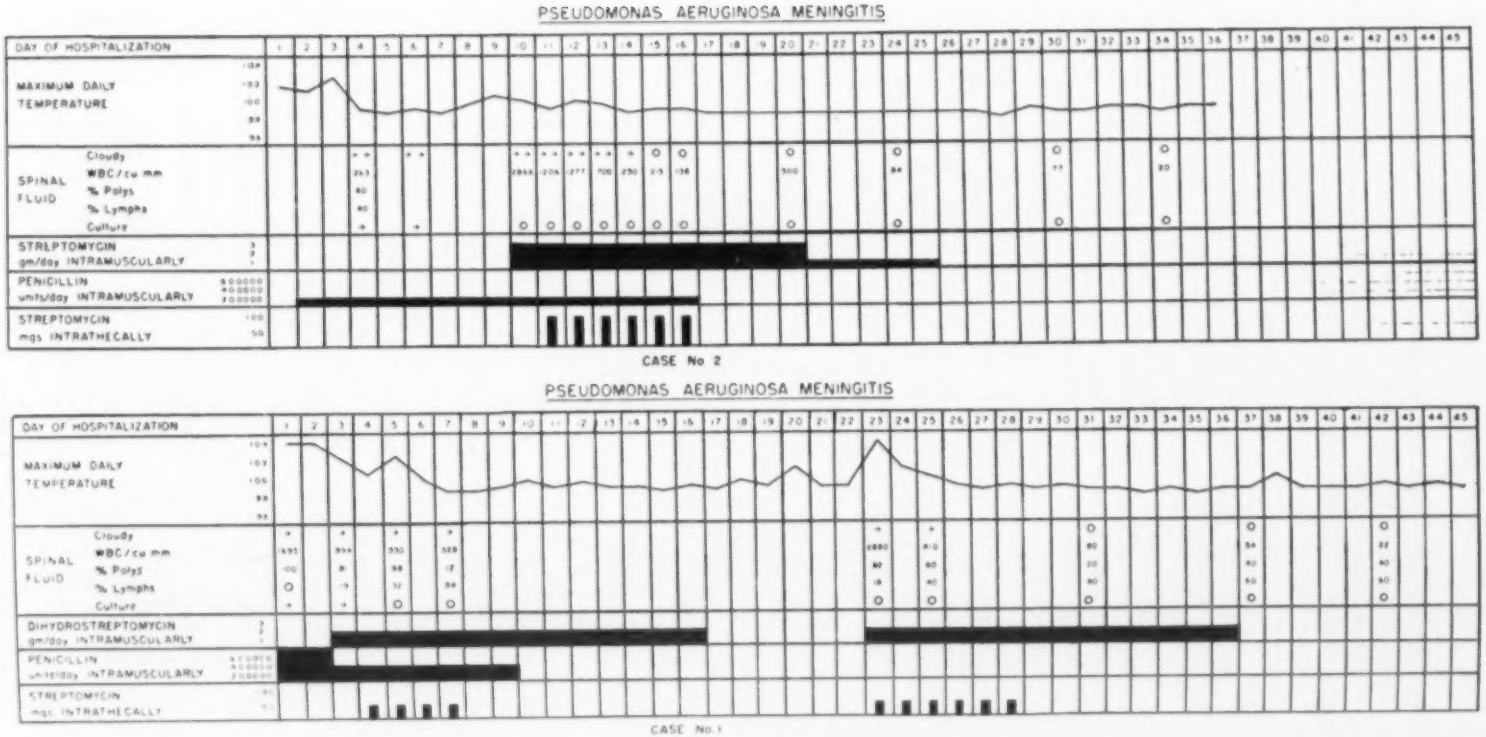

FIG. 1.

gradually. She was closely observed until April 26, and at no time were toxic manifestations of streptomycin therapy noted. One month later the patient was still well.

Case 2. A 57 year old male was admitted to the Woman's Medical College Hospital on September 14, 1947, five weeks following a hemorrhoidectomy under spinal anesthesia at another hospital. Ten days postoperatively he had developed severe suboccipital pain, attributed by his physician to the spinal anesthesia. The following day he became febrile and was treated for "pneumonitis" with sulfonamides. He remained asymptomatic until two days before admission, when he complained of anorexia, malaise, headache, aching extremities and low grade fever. His temperature rose to 102° F. and penicillin therapy was instituted. There was no apparent response and he was hospitalized, complaining of pain in the back of the neck radiating to the eyes and forehead. On initial physical examination, the only significant finding was post-tussive râles in the right midlung field. The patient continued to have intermittent pain in the back of the neck and down the legs. Urinalysis was negative. Hemoglobin was 12.5 gm., white blood count 9,450, with 80 per cent polymorphonuclears, 18 per cent lymphocytes and 2 per cent monocytes. Stool examination and culture were negative for pathogens, and agglutinations for typhoid, paratyphoid, brucellosis and Proteus X19 were negative. Blood cultures on September 14 and 16 showed no growth. Tuberculin test with purified protein derivative and roentgen-ray examination of the chest were negative.

On September 17 lumbar puncture revealed a yellowish-green opalescent fluid containing 263 cells per cu. mm., of which 60 per cent were lymphocytes and 40 per cent polymorphonuclears (figure 1). No organisms were identified on direct smear, but *Pseudomonas aeruginosa* was cultured. Another positive culture for this same organism was obtained on September 19. On September 23 the spinal fluid cell count was 2,866 per cu. mm.

Streptomycin was administered in doses of 2.8 gm. per day intramuscularly from September 23 to October 3. The dose was then reduced to 1 gm. per day and continued until October 8. Intrathecal doses of 100 mg. were given daily from September 24 to 29. The patient was also given 25,000 units of penicillin every three hours from September 15 to 29.

There was progressive clinical improvement. When the patient became ambulatory, however, he complained of unsteady gait which persisted until his discharge on October 19. Subsequent examination a year later indicated that he had persistent vestibular dysfunction.

Discussion

The two cases presented illustrate the recognized view that the common mode of infection with *Pseudomonas aeruginosa* meningitis is by direct contamination of the spinal subarachnoid space. This emphasizes the importance of the prophylaxis against this serious infection. Increased care is essential in the preparation of equipment and solutions for lumbar puncture, spinal anesthesia and intrathecal therapy. Particularly to be condemned is the cold sterilization of spinal fluid needles in alcohol.[7]

Although streptomycin is the most effective agent to date in the treatment of *B. pyocyaneus* infections, the mortality rate remains high. The effectiveness of the drug is further limited by the high degree of toxicity encountered when doses adequate to control an infection are used. Substitution of dihydrostreptomycin for streptomycin reduces the toxicity of the drug,[8] and it has been shown in the treatment of tuberculosis that reduction of the dose of streptomycin lowers the

incidence and severity of toxic reactions.[9] When sensitive strains of *Pseudomonas aeruginosa* are treated, such reduction of dosage is feasible. The sensitivity of this organism to streptomycin varies from 2.5 to 25 micrograms per cubic centimeter, but strains resistant to 256 micrograms per cubic centimeter have been reported.[10] When resistant strains are encountered, the high mortality of the infection justifies the risk of large doses.

There are obvious objections to the use of an irritating drug in direct contact with the meninges. Frequent intrathecal injections of streptomycin were followed by a secondary febrile response associated with increase in protein and cells in the cerebrospinal fluid,[5] and excessively large individual doses are known to produce serious reactions.[5, 5] The intrathecal use of streptomycin is based upon studies showing that very little streptomycin diffuses into the spinal fluid following intramuscular injection.[10] Dihydrostreptomycin is even more irritating than streptomycin and is not suitable for intrathecal use.[8] The recommended intrathecal dose of streptomycin is 25 to 100 mg. in 5 to 10 c.c. every 24 hours.

SUMMARY

1. Two cases of primary *Pseudomonas aeruginosa* meningitis following spinal anesthesia were successfully treated with intramuscular and intrathecal streptomycin.

2. The danger of meningeal infection resulting from improperly prepared lumbar puncture equipment or solutions for intrathecal use is stressed.

3. Streptomycin is the most effective agent to date in the treatment of *Pseudomonas aeruginosa* meningitis.

ACKNOWLEDGMENT

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THE ARREST OF RECURRENT EMBOLISM DUE TO AURICULAR FIBRILLATION WITH MITRAL STENOSIS BY QUINIDINE–ANTICOAGULANT THERAPY*

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A SERIOUS and often fatal complication of auricular fibrillation, especially when associated with mitral stenosis, is the production of intraauricular thrombosis and embolism. When embolism is recurrent, the condition is likely to be fatal unless normal auricular contractions are restored and the source of emboli is thereby eliminated. Although restoration of normal rhythm by quinidine therapy has been recommended generally in the treatment of uncomplicated auricular fibrillation of short duration, there is a natural hesitation among many physicians to employ this drug in the presence of long established auricular fibrillation with repeated embolic episodes complicating serious heart disease because of the fear that termination of the arrhythmia will cause death or other critical consequences by dislodging another embolus.

The development of anticoagulant therapy has made it possible to check the formation of emboli within the auricles. When this is accomplished, there should be reasonable assurance that restoration of normal rhythm will not cause dislodgement of another embolus. Two cases in which treatment was used successfully in this manner are reviewed. Both patients, previously considered to have a fatal prognosis due to a persistently recurrent embolism, now have been free of this complication for 15 and 11 months, respectively. Review of the literature has not revealed any similar reports of the successful use of combined quinidine-anticoagulant therapy in this condition.

CASE REPORTS

Case 1. A 43 year old white woman was admitted to the Jefferson Hospital on April 21, 1948, because of numerous infarctions of the spleen, mesentery, legs and brain which had occurred over a period of 11 months. It was assumed that these infarctions resulted from emboli which were dislodged from a thrombus located in the left auricle of the heart; and further that the thrombus formation was a result of auricular fibrillation associated with stenosis.

The patient had been known to have heart disease since the age of five years, when she had had an attack of chorea. There had been no apparent recurrences of rheumatic infection and no symptomatic manifestations of cardiovascular impairment until May, 1947. At that time she began to have recurrent attacks of severe ab-

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dominal pain, with nausea, vomiting and diarrhea. In June she was admitted to another hospital, where a diagnosis of heart disease and splenic infarction was made. She was given digitalis and, on subsidence of the attacks, was discharged. The attacks recurred in July and she was admitted to the Jefferson Hospital, where a similar diagnosis of rheumatic heart with mitral stenosis, auricular fibrillation and splenic infarction was made. In two weeks she was discharged. She entered a third hospital in November, 1947, with recurrence of the attacks and, because of severe, intractable pain in the left upper abdomen, a splenectomy was performed. Symptomatic relief was obtained, although she subsequently had recurrent episodes of pain in the right upper quadrant. One week later, however, an embolus lodged in the right internal iliac artery and an embolectomy was performed successfully. In February, 1948, she again was admitted to another hospital with a diagnosis of arterial embolism in the left leg. She recovered in two weeks on conservative treatment. Approximately one week after recovery from this attack, she had an episode of transient numbness of her entire right side except the face. She was re-admitted ultimately to the Jefferson Hospital, following another episode of cerebral embolism manifested by transient numbness of the left side. On admission the previous symptoms had subsided and she had no complaints except for occasional excessive breathlessness on exertion. She had been taking 0.1 mg. of digitoxin daily for the past 10 months.

Physical examination revealed a well developed but rather thin white woman who did not appear acutely ill. There were no signs of congestive heart failure. The heart appeared enlarged, its left border being approximately 3 cm. outside the midclavicular line in the fifth intercostal space. The cardiac rhythm was completely irregular and the ventricular rate averaged 84. The first sound at the apex was accentuated and an opening mitral snap was audible. A rumbling diastolic murmur and a diastolic thrill were present at the apex. On the abdomen there were three well-healed surgical scars. The left foot was cooler than the right and the pedal pulses could not be felt.

Laboratory studies were as follows: red blood count, 4,450,000; hemoglobin, 12.5 gm.; white blood count, 13,600, with a normal differential count; platelet count, 292,000; venous blood coagulation time, seven minutes; bleeding time, two minutes; prothrombin time (Quick method), 86 per cent of normal; Wassermann and Kahn reactions, negative; urinalysis, essentially normal; blood urea nitrogen 14.4 mg. per cent; total serum proteins, 6.89 gm. per 100 c.c.—albumin, 3.69 gm., and globulin, 3.2 gm.; serum bilirubin, 0.5 mg.; no bromsulfalein retention. By fluoroscopic and roentgen-ray examination the heart presented a typical mitral configuration, and the transverse diameter of the heart was approximately 25 per cent greater than the predicted normal. The lung fields appeared normal. An electrocardiogram made on admission revealed auricular fibrillation with a ventricular rate of 78 beats per minute.

The diagnosis on admission was rheumatic heart disease with cardiac enlargement, mitral stenosis, auricular fibrillation and intraauricular thrombus with recurrent embolism. It was recommended by the hematologic and cardiac consultants* that an attempt be made to arrest intraauricular embolus formation by heparin therapy, and then to restore normal sinus rhythm by the use of quinidine. The procedure chosen was to maintain the venous clotting time at a satisfactory therapeutic level (at least 30 minutes in a glass tube or 60 minutes in a collodion-lined tube) for three weeks. Because of the use of an experimental preparation of heparin in a gelatin menstruum, the preliminary period of heparinization was prolonged to six weeks, and oral medication with caronamide was required before a satisfactory therapeutic level was maintained for the desired period. Quinidine therapy was

* Dr. Leandro Tocantins and Dr. Louis B. Laplace.

begun with a preliminary dose of 0.2 gm. The patient was given 0.4 gm. orally every two hours for five doses with no apparent effect. The dosage was increased to 0.6 gm. every two hours for a total of five doses on each of the following three days. On the fourth day of quinidine therapy, sinus rhythm with a second degree heart block and a Wenckebach phenomenon with occasional dropped beats was demonstrated by an electrocardiogram. During the following three days a total dose of 2.4 gm. of quinidine was given. The same rhythm was maintained until the sixth day of quinidine therapy, when an auricular flutter developed. After administration of 1.2 gm. of quinidine, regular sinus rhythm returned. A total dosage of 2.4 gm. was given on that day. The following morning, auricular fibrillation recurred. The patient was given a total of 1.8 mg. of digitoxin in six hours, and on the next day, in addition to 0.2 mg. digitoxin, she received quinidine sulfate, 0.6 gm. every three hours for five doses. During the next two days, quinidine medication was discontinued because of nausea, but a maintenance dose of 0.1 mg. of digitoxin was continued. On the thirteenth day after the initiation of therapy, quinidine sulfate again was given, in a dosage of 0.4 gm. every three hours. The digitoxin was discontinued three days later. After five days of this régime an electrocardiogram demonstrated normal sinus rhythm with P–R intervals of 0.26 second. The quinidine dosage was reduced to 0.2 gm. every six hours on the following day. Heparin therapy was then discontinued. The normal sinus rhythm persisted.

On the twenty-first day after the initiation of quinidine therapy, and the fourth day after the restoration of normal sinus rhythm and the discontinuation of heparin therapy, the patient complained of a severe headache and nausea, and vomited all ingested material. Quinidine medication was discontinued because it was thought that it might be responsible for these symptoms. On the next day the patient complained of intermittent abdominal cramps. There was moderate generalized abdominal tenderness. The nausea and vomiting continued and, in addition, a watery diarrhea developed. On the following day the abdominal cramps became much more severe, the temperature rose to 101° F., a firm tender mass became palpable in the right lower quadrant and abdominal distention developed. A roentgenogram of the abdomen was suggestive of an obstruction of the small bowel. A Miller-Abbott tube was passed and continuous suction maintained. Heparin therapy was reinstituted and given intravenously in a solution of 5 per cent glucose in physiologic saline solution continuously at a dosage and rate sufficient to maintain a minimal venous blood clotting time of 30 minutes in a glass tube or 60 minutes in a collodion-lined tube. In addition, the patient was supported with ascorbic acid, vitamin K and fluids given intravenously. Vitamin K was added after a steady decrease of the fasting prothrombin time from 71 per cent of normal on the fourth day to 12 per cent of normal on the ninth day. The prothrombin time gradually returned to normal after institution of vitamin K therapy, and oral feeding was resumed. The patient responded to the treatment and improved steadily. After 11 days the Miller-Abbott tube was removed and the patient ate a soft diet without difficulty. Five days after the quinidine therapy had been discontinued, auricular fibrillation recurred and 0.2 gm. of quinidine again was given every four hours. The following day, normal sinus rhythm returned and persisted thereafter. The quinidine sulfate dosage was reduced to 0.2 gm. every six hours on the third day and maintained at that amount for eight more days until one week before discharge, when it was discontinued. Heparin therapy was discontinued 18 days after it was reinitiated and two days before discharge.

At the time of discharge, approximately three months after admission, the patient had been sitting in a chair for two days. She was greatly improved. Normal sinus rhythm had persisted for two weeks and the electrocardiogram was normal except for

P–R intervals of 0.24 second, prolongation of the Q–T interval (K = 0.599 second) and low voltage of the T-waves in Lead I.

One year later the patient still has a normal sinus rhythm and there has been no recurrence of emboli. At intervals of one to two months her family physician, Dr. Gaetano Brindisi, has prescribed a small maintenance dose of quinidine for periods of five to six weeks because of numerous premature contractions. She is ambulatory, appears well and has gained 35 pounds in weight. Her only complaints are of mild dyspnea and pains in her legs following moderate exercise. The signs of mitral stenosis are unchanged. There is evidence of impaired circulation in the legs. The only abnormal finding in the electrocardiogram is a prolongation of the P–R intervals to 0.28 second. The improvement in her general appearance and attitude is striking.

Case 2. An unmarried 39 year old white woman was admitted to the Jefferson Hospital on October 31, 1948, because of stupor and left facial weakness.

This patient had first been seen by one of us (E. L. H.) on July 31, 1947, when she came to the office complaining of shortness of breath and swelling of the ankles. Abnormal breathlessness when climbing stairs and walking fast on the level had first occurred 10 years previously. Seven years later ankle edema appeared for the first time, and dyspnea became worse progressively until it occurred after walking only one-half block. Palpitation, tachycardia and precordial pain were present on relatively slight effort. At night it became necessary for the patient to sleep in a semi-recumbent posture on three or four pillows. She had frequent prolonged "colds."

At the age of two years the patient had had severe diphtheria. When she was 10 years old her tonsils were removed. At the age of 16 she had an episode suggestive of rheumatic fever, with pains in her right shoulder and in both knees. A diagnosis of fallen arches was made at that time.

Physical examination prior to hospitalization revealed a thin, pale woman who appeared mildly dyspneic at rest. Pertinent abnormalities were tachycardia of 100 per minute, a few coarse moist râles in the lower right chest posteriorly, cardiac enlargement with the apex beat palpable in the sixth intercostal space at the anterior axillary line, systolic and diastolic murmurs at the mitral area, and slight ankle edema.

A diagnosis was made of rheumatic heart disease with mitral stenosis and insufficiency and congestive failure, and the patient was admitted to the Jefferson Hospital for the first time. Laboratory studies were within normal limits. The arm-to-tongue circulation time was 25 seconds, and the venous pressure was 165 mm. of water. A roentgenogram of the chest showed a marked cardiac enlargement to the left and prominence of the pulmonary conus. The transverse diameter of the heart measured 17 cm. (predicted normal, 11.5 cm.). Evidence of pulmonary congestion was present. An electrocardiogram showed notched and spread P waves and a pronounced right axis deviation. The patient improved following complete bed-rest and administration of digitalis, ammonium chloride and a low sodium diet (500 mg. daily). She was discharged, much improved, in 10 days.

After discharge she remained comparatively well until the occurrence of a cold in January, 1948. About four weeks later she had a transient attack of periumbilical pain, followed in a few days by a fleeting pain in the left upper quadrant. On March 15, 1948, an attack of paroxysmal tachycardia occurred which lasted 10 hours. An electrocardiogram taken two days later revealed no significant change.

In May, 1948, several short episodes of tachycardia occurred and ankle edema reappeared. In July, 1948, while at the seashore on vacation, she suffered severe pain in the right upper abdomen over a period of two weeks. On October 4, numbness, coldness and pain appeared in the right leg. The right dorsalis pedis pulse was barely perceptible. Papaverine hydrochloride, 0.05 gm., was prescribed every four hours. In a few days the circulation returned to normal.

On October 24, 1948, one week before admission, the patient stayed home from work and went to bed because she thought she had a "heavy chest cold." Fever, cough and rather severe pains were present in the right chest and later in the left chest. On October 31, just after returning to her bed from the bathroom, she suddenly became stuporous and the left side of her face sagged. The family physician was summoned and he advised immediate hospitalization.

Physical examination on admission to the hospital revealed a dyspneic, orthopneic, acyanotic, well developed but thin white woman who appeared ill. The mucous membranes were pale. There were coarse, moist râles in both lung bases. The heart was enlarged, with the apex in the left midaxillary line. The rhythm was completely irregular. Systolic and diastolic murmurs were heard at the apex. The liver was palpable two fingerbreadths below the right costal margin. The spleen was not palpable. There was muscular weakness of the left side of the face excluding the forehead.

Laboratory studies were as follows: red blood count, 3,200,000; hemoglobin, 10.4 gm. (68.1 per cent); white blood count, 13,600, with a normal differential count; prothrombin time (Quick method), 30 per cent of normal; urinalysis, normal; blood sedimentation rate (Wintrobe), 31 mm. in one hour.

A roentgenogram of the chest demonstrated an enlarged heart with a prominent pulmonary conus, and evidence of bilateral pulmonary congestion with a small amount of fluid in the bases of both pleural cavities. An electrocardiogram showed auricular fibrillation, with an average ventricular rate of 65, a right ventricular strain pattern and digitalis effect.

A diagnosis was made of rheumatic heart disease with cardiac enlargement, mitral stenosis and auricular fibrillation, and cerebral embolism with facial paralysis.

On admission, anticoagulant therapy was started immediately. During the first 48 hours the patient received intravenously five to 10 drops per minute of a solution of 500 c.c. of 5 per cent glucose containing 200 mg. of heparin, which maintained a coagulation time of approximately 30 minutes in a glass tube or 60 minutes in a collodion-lined tube. Dicumarol therapy also was initiated, with the administration of 300 mg. orally on the first day and a sufficient amount on subsequent days to maintain a prothrombin time (Quick method) of less than 20 per cent of normal.

The daily maintenance dose of 0.2 mg. of digitoxin was continued. On the fourteenth hospital day the decision was made to attempt to halt the embolic episodes by restoring normal sinus rhythm with quinidine therapy. After an initial dose of 0.2 gm., quinidine sulfate was given in an increasing dosage of 0.2 gm. twice daily the first day, 0.2 gm. three times daily the second day, 0.3 gm. three times daily the third and fourth days, and 0.3 gm. four times the fifth day. On the sixth day of quinidine therapy, when the quinidine dosage had been increased to 0.3 gm. every four hours for six doses per day, normal sinus rhythm returned and was demonstrated by an electrocardiogram which revealed, in addition, prolonged A–V conduction. Quinidine medication was continued at a dosage of 0.3 gm. twice daily. Digitoxin, 0.2 mg. daily, also was continued.

Dicumarol therapy was stopped seven days after the restoration of normal rhythm, and the patient was discharged in an improved condition and with no evidence of facial paralysis. She was able to walk short distances without tachycardia or dyspnea. The quinidine and digitoxin therapy was maintained.

After discharge, the patient was in very good health with regular cardiac rhythm until May 17, 1949, when, after returning home from a weekend at the seashore, she walked upstairs and developed precordial pain. Upon awakening the next morning, she noticed rapid heart action. This disappeared after seven or eight hours. Irregular rhythm reappeared on May 31, 1949, at which time an electrocardiogram revealed an impure flutter fibrillation with a ventricular rate of approximately 90.

Quinidine sulfate was increased to 0.2 gm. three times a day. Normal sinus rhythm was reëstablished, and at the present time the patient is in good condition. She has had no recurrence of emboli. Quinidine is being continued in daily maintenance dosage of 0.2 gm. twice daily.

Discussion

These cases emphasize certain points regarding the use of quinidine for the termination of auricular fibrillation. Although the use of quinidine in similar cases has been reported and recommended,[1, 2, 3, 4, 5, 6, 7] the belief still seems prevalent that quinidine is indicated only when there is no serious organic heart disease, when the arrhythmia is of relatively brief duration, and when there has been no embolism. It is undoubtedly true that, as a rule, the more advanced the degree of structural abnormality of the heart, particularly when mitral stenosis is involved, the less likely the success in restoring normal sinus rhythm, especially for any worthwhile period of time. Whether long duration of auricular fibrillation decreases the chances of restoring normal rhythm, except insofar as the structural disease of the heart is progressing during this period, is questionable.

The degree of risk involved in restoring normal rhythm in the presence of auricular fibrillation with embolic phenomena is not known. Some [1, 2, 6] believe that the incidence of embolism following the use of quinidine is no greater than is to be expected in those cases in which it is not used.

The cases presented demonstrate clearly that when much can be gained by the restoration of normal sinus rhythm by the use of quinidine, it should be attempted under even adverse circumstances. Persistent therapeutic effort in such cases is more often successful than is generally appreciated.

The use of anticoagulant therapy before attempting to restore normal rhythm in the presence of recurring emboli is at least theoretically indicated. It is not to be expected that an organized intraauricular thrombus will be "dissolved" by heparin or Dicumarol. Fortunately, however, the majority of such thrombi are firmly adherent to the endocardium and are seldom dislodged by the resumption of normal auricular contractions. Those clots which usually break off as emboli are the friable elements of thrombus formation, and it is these which are favorably affected by anticoagulants. The danger of the dislodgment of such clots may be expected reasonably, therefore, to be minimized by the preliminary administration of heparin and/or Dicumarol. It is realized, however, that definite conclusions cannot be made on the basis of so few cases.

How long anticoagulant therapy should be continued before attempting to abolish the fibrillation is, of course, uncertain. It obviously depends somewhat on how effectively the clotting mechanism of the blood is inhibited in the individual case. In the two cases presented, the preliminary duration of anticoagulant therapy was based on the personal experience and judgment of the hematologic consultant, who felt, however, that in other cases a shorter period—of perhaps seven to 10 days—might be adequate.

Summary and Conclusions

Two cases are reported in which recurrent and potentially fatal embolism, due to auricular fibrillation and rheumatic heart disease with mitral stenosis, was terminated following the successive administration of anticoagulant therapy to in-

hibit intraauricular clotting and of quinidine therapy to restore normal sinus rhythm. In cases of embolism due to auricular fibrillation, it may be possible to minimize the danger of dislodging another embolus during the restoration of normal rhythm by a preliminary period of anticoagulant therapy. The unquestionable value of quinidine therapy in such cases is again demonstrated.

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PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY: A CASE REPORT *

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Muscular dystrophies are by no means uncommon, but the occurrence of a case which so clearly illustrates the heredofamilial nature of this disease, as well as associated disturbances in creatine-creatinine metabolism, warrants discussion. Recently such a case presented itself on the Isolation Service at University Hospital. This case was admitted because of an acute meningococcic meningitis with meningococcemia. The muscular dystrophy with accompanying pseudohypertrophy was obvious at once, and later findings substantiated the initial impression.

Case Report

A 10 year old white male was admitted to the Isolation Service of University Hospital on January 8, 1949. His parents did not accompany him, and the history as obtained from the grandmother was brief and incomplete insofar as the present illness was concerned. The patient had apparently been well until several months prior to admission, at which time he began to receive injections of an unknown drug designed to prevent him from becoming a "cripple," as had two maternal uncles who had died at an early age from a progressive muscular abnormality. Although the patient had been asymptomatic at the onset of treatment, he began to complain of

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weakness in his legs one month later. He was able to continue in school and was doing well scholastically. Forty-eight hours prior to admission, while attending classes, he developed generalized muscle aches and pains, nausea and vomiting, and elevation of temperature to 104° F. He was taken home, and the next day he appeared to be no better. The morning of the day of admission it was noted that he was semicomatose, irritable and apparently acutely ill. He cried out often as if in pain, and his grandparents, with whom he was staying at the time, noted multiple scattered purplish-red "spots" over his entire body. A local physician was called who recommended immediate hospitalization, and the patient was admitted several hours later for observation and treatment.

The patient had had no previous hospitalizations or serious illnesses. He had had the usual childhood diseases. He was a full-term normal infant at birth and was delivered spontaneously without apparent difficulty. There was a remarkable familial history, obtained from the patient's grandmother, of an apparently sex-linked progressive muscular disease transmitted only by the female side of the family

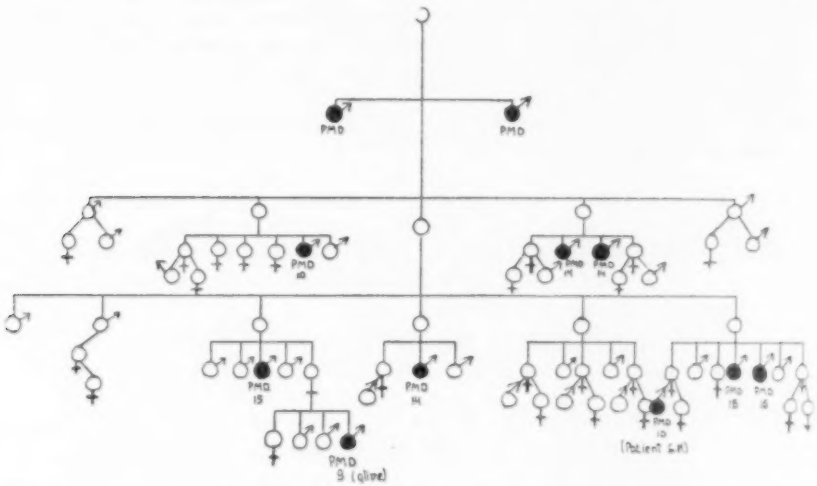

FIG. 1. Genealogic tree of patient S. H. PMD—progressive muscular dystrophy. Numeral indicates age at death. Of 11 cases, only two are alive at present time.

and involving certain males of at least four generations. (See figure 1.) Eleven males were affected; seven died before the age of 18, two were alive at the time of this report.

Physical examination revealed a well developed, well nourished white male lying in a semicomatose state in bed. Opisthotonos was immediately apparent. The temperature was 103.4° rectally, pulse 100 and respirations 26. The blood pressure was 100 mm. Hg systolic and 70 mm. diastolic. The skin was cool, pale and dry. Over the entire body, with a predilection for the extremities and face, was a hemorrhagic exanthema consisting of multiple petechial to ecchymotic sized areas. There were a few fresh gingival hemorrhages. The lungs were clear and resonant anteriorly and posteriorly to auscultation and percussion. The heart rate was rapid, with a marked sinus arrhythmia; the sounds were clear and of good quality. Examination of the extremities showed a nonpitting enlargement of both calves and of the feet and ankles. The musculature was soft, flabby and atonic. There was marked atrophy of both shoulders and early winging of the scapulae. There was a typical "tapir-

like" facies. (Later in the hospital course, when the patient was well enough to be out of bed, lumbar lordosis was noted, as well as a peculiar rolling gait. Gowers' sign was present as the patient attempted to rise from a supine position.) Neurologic examination revealed marked nuchal rigidity, with positive Kernig's and Brudzinski's signs. The deep and superficial reflexes were absent. Babinski's and Hoffmann's signs were negative, as were the Oppenheim reflex and Chaddock's reflex. Sensory acuity could not be tested.

Initial blood count revealed 4.56 million red cells, with 11.4 gm. of hemoglobin. There were 14,350 white blood cells, with 93 per cent neutrophils, 4 per cent lymphocytes, 1 per cent monocytes and 2 per cent eosinophils. Initial urinalysis showed 20 mg. per cent albumin, 0 to 5 red blood cells per high power field, and 4 plus acetone. Spinal tap done immediately following admission gave the following information: Initial pressure was 470 mm. H_2O, and final pressure after approximately 12 c.c. of fluid were withdrawn was 240 mm. H_2O. The fluid was grossly purulent. There were 5,050 white blood cells per cu. mm. and 160 red blood cells per cu. mm. The differential showed 78 per cent polymorphonuclears and 22 per cent lymphocytes; sugar was 23 mg. per cent. Two spinal taps done the day after admission showed approximately the same findings. Smear and culture of the spinal fluid and blood cultures revealed organisms resembling *Neisseria intracellularis*. On the third hospital day, creatine and creatinine studies were undertaken. The blood levels of creatine and creatinine were 1.97 mg. per cent and 1.1 mg. per cent, respectively. Urine studies showed a 24 hour excretion of 3.94 mg. per cent of creatine and 2.57 mg. per cent of creatinine. On the tenth hospital day, creatine tolerance studies were begun. On a standard diet containing 1.32 gm. of creatine hydrate (equivalent to 1 gm. of creatine), the patient excreted 28.5 mg. per cent of creatine and 20.8 mg. per cent of creatinine in 24 hours. On the sixteenth hospital day these studies were repeated; this time the urinary excretion of creatine over 24 hours was 52.2 mg. per cent and that of creatinine was 30.0 mg. per cent. A normal control on the same diet excreted 0.046 mg. per cent of creatine in 24 hours.

Other blood chemistry studies revealed a blood phosphorus level of 4.0 Bodansky units; blood calcium, 9.0 mg. per cent, and blood urea nitrogen, 9.5 mg. per cent. The blood Wassermann and Kahn, as well as spinal fluid Wassermann and Kahn, were negative.

Hospital Course: Immediately following admission laboratory work, the patient was started on penicillin, 100,000 units every three hours, as well as 5 gm. of Na sulfadiazine intravenously stat and 4.2 gm. intravenously every four hours thereafter for three doses. The patient was also given water, glucose and saline intravenously, and adrenal cortical extract to combat any tendency toward adrenal collapse. It was necessary to insert a Foley catheter into the bladder as the patient was incontinent. Small amounts of sedatives were given because of extreme restlessness. Twenty hours after admission the dose of sulfadiazine given intravenously was cut from 4.2 gm. to 1 gm. every six hours, and then to 1 gm. every eight hours. The patient exhibited slow but steady improvement, and on the fourth hospital day aqueous penicillin was discontinued and duracillin begun, 1 c.c. daily. The intravenous sulfadiazine was also discontinued and oral sulfadiazine started. The patient received a total of 10,200,000 units of penicillin in the first three days and 21.6 gm. of sulfadiazine in the same period of time. The temperature course was steadily downward, reaching a normal level on the tenth hospital day and remaining there for the rest of the hospital stay. Duracillin was discontinued on the seventh hospital day and sulfadiazine on the thirteenth hospital day. On the fifteenth hospital day the patient was removed to the operating room on the isolation ward and a biopsy of the left thigh and right calf taken. The muscle was very pale and edematous in the calf region, and in the thigh it appeared as though the muscle had been replaced by yellowish hard fatty

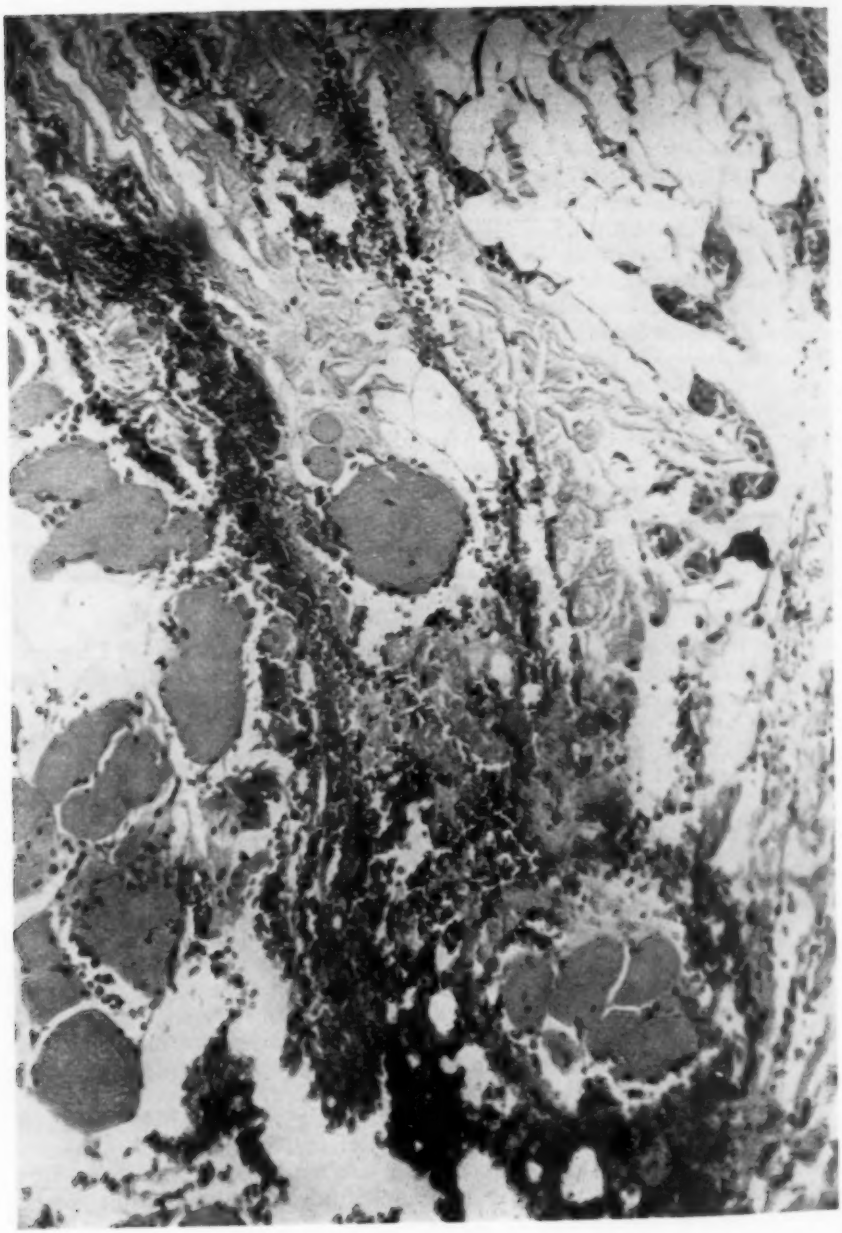

FIG. 2. Specimen taken from the left thigh. Note fatty infiltration and partial hyalinization. Grossly, lipomatous pseudohypertrophy was marked.

tissue with few muscle strands remaining. Pathologic study of these sections revealed fatty infiltration between the muscle fibers, with fragmentation and partial hyalinization. There was an increase in connective tissue irregularly distributed peripherally and between the muscle fibers. The fibers were split away from the sarcolemmal sheath in several areas.* (See figure 2.) The patient was discharged on the twenty-first hospital day, with instructions to continue medical care with his local physician. Glycine was recommended as treatment for the muscular dystrophy. At the time of discharge the purpuric lesions had cleared with but little necrosis. The neurologic signs had vanished.

Discussion

The first discussion of progressive muscular dystrophy was by Meryon [1] in 1852, and it was followed by a similar discussion by Duchenne [2] in 1861. In 1884 Erb [3] was the first to differentiate between muscular dystrophies and atrophies, and he described a spinal form of muscular atrophy with degeneration of the anterior horn cells and muscular dystrophy in which no such changes were seen. Numerous clinical types of progressive muscular dystrophy have been described. Erb described a juvenile type which occurred later in childhood and was not accompanied by pseudohypertrophy. A facioscapulohumeral form was described by Landouzy and Dejerine which included facial musculature involvement as well as changes noted by Erb. Although the earliest descriptions of the disease mentioned involvement of the proximal musculature, Gowers [5] in 1879 stated that there was a form of the disease with early changes seen in the distal musculature.

The changes in progressive muscular dystrophy are limited for the most part to the skeletal muscles, although myocardial involvement has been reported.[6, 7] The smooth muscle appears to be uninvolved. Pseudohypertrophy appears to involve chiefly the large skeletal muscles, such as the gastrocnemius, soleus, gluteus, deltoid, supraspinatus and infraspinatus, and muscles of the tongue. The disease is a heredofamilial disease. Polacheck presented the genealogic tree for a family in which 10 male members in three generations had progressive muscular dystrophy. The disorder was clearly seen to be a sex-linked Mendelian recessive. It occurred only in the male descendants of unafflicted female carriers and, in this respect, resembled hemophilia.[8] Weitz [9] noted that the dominant form of transmission was accompanied more frequently by involvement of muscles of the upper extremity, while the disease manifesting itself in dystrophy involving the lower extremities was more often recessive. There appears to be no specific age group involved. Cases have been reported in all decades, but children are most frequently affected. There is no particular predilection for race, nationality or social level.

Pathology

The muscles affected by dystrophy are pale, firm and shiny. Microscopically there is an increase in the amount of connective and fatty tissue between the muscle fibers. The fibers are decreased in volume and may show longitudinal splitting. Accumulations of nuclei appear beneath the sarcolemmal sheaths. Within the muscle fibers one may see hyaline and granular degeneration and, in

* See acknowledgment p. 1156.

the late stages of the disease, the muscle is almost completely replaced and only occasional fibers are seen. The internal perimysium seems more richly nucleated, more markedly developed, and frequently changed into fatty tissue. This lipomatosis of the connective tissue leads to a lipomatous pseudohypertrophy of the atrophic muscle.[10]

Signs and Symptoms

Examination of patients with the pseudohypertrophic form of the disease reveals pseudohypertrophy most frequently of the gastrocnemius, soleus, gluteus, deltoid, supraspinatus and infraspinatus. If the facial muscles are involved, the typical "tapir-like" facies is noted, especially if the patient is asked to smile. Involvement of the shoulder muscles results in winging of the scapulae. Lumbar lordosis is seen with involvement of the lumbar musculature. Involvement of the muscles of the lower extremities results in a characteristic gait in which the feet are slapped down and the hips rolled one ahead of the other in an effort to propel the body forward. Almost all young patients with this disease show the sign of Gowers when attempting to arise from a supine position. The patient will be seen to turn over, rise to a kneeling position and, by a process of climbing up on himself, gain the upright position. Fibrillary twitchings of the affected muscles are not seen. In contrast to spinal myopathy, reactions of degeneration are not found. The electrical activity of the diseased muscle is quantitatively diminished. Neurologic examination is essentially negative except for occasional hypoactivity and even absence of the deep tendon reflexes. Often in early stages of the disease involving the lower extremities the Achilles tendon reflex is hyperactive. Signs and symptoms referable to the heart are absent unless myocardial involvement has occurred. Roentgenologic changes, consisting of delayed appearance of the centers of ossification in the bones of the hands and in the epiphyses of the long bones, and demineralization have been reported and are even considered characteristic of this disease by Shank et al.[11] Epstein and Abramson reported seven cases in which alterations in roentgen-ray appearance of the long bones and scapulae were seen in six and of the pelves in all seven. The most constant changes were (*a*) symmetric diminution in the size of the scapulae, (*b*) rather large humeral heads in relation to the small, shallow glenoid fossae, (*c*) slender humeral shafts, in some instances approaching the "pipe-stem" appearance, with widened medullary canals and thin, but not atrophic, cortices, and (*d*) in several instances, disproportionately slender femurs, tibias, fibulas, radii and ulnae, which showed the same changes as seen in the humeri. It was their belief that these changes represented mesodermal defects and could not be explained on the basis of disuse alone.[12] Laboratory data are not helpful except for studies of creatine and creatinine metabolism.

Creatine and Creatinine Metabolism

The significance of disorders of creatine and creatinine metabolism in progressive pseudohypertrophic muscular dystrophy is unknown. The normal adult male excretes from 1.2 to 1.8 gm. of creatinine in the urine every 24 hours. Although this may vary widely from person to person, the amount excreted by any one person remains remarkably constant.[13] The output of creatinine is di-

rectly related to the total mass and efficiency of muscle, but there is no relationship between creatinine excretion and the concentration of creatine in the muscle.[14] Early observations, later confirmed, showed that there is a diminution in the amount of creatinine excreted in muscular dystrophy. The diminution in the creatinine excretion is often greater than the apparent reduction in functional muscle mass.[15] Observations that the creatinine output is proportional to the muscle mass are probably true, but Milhorat and Wolfe [16] have pointed out that it is probably proportional to the efficiently functioning muscle mass rather than to the amount of muscle per se.

The normal adult male eliminates considerable amounts of creatinine in the urine but no creatine. However, infants and children excrete large amounts of creatine normally. All investigators of muscular dystrophy have observed creatinuria of fairly large amounts in this disease. Thus a true picture of the inherent metabolic disorder in children is difficult to obtain, for children without as well as those with the disease may show marked creatinuria. Hence it becomes necessary to rely upon creatine tolerance studies, especially in infants and children with muscular dystrophy.

When creatinine is administered it is promptly excreted almost completely, but the normal organism is capable of retaining considerable amounts of ingested creatine without effect on the urinary constituents.[17] In patients with muscular disease the ability to retain ingested creatine is often impaired. Diminished creatine tolerance in progressive muscular dystrophy has been observed by numerous workers. Thus the creatine tolerance test is a better index of the extent of the metabolic defect than is the level of the spontaneous output of creatine. In progressive muscular dystrophy the impairment in the creatine tolerance is usually greater than in patients with a comparable amount of muscular wasting due to lesions of the peripheral nerves or spinal cord. One may wonder if there is not some factor present in the so-called "normal" remaining muscle that accounts for the decreased creatine tolerance.

It has been shown that the excretion of urinary creatinine is increased when normal subjects and dogs ingest large amounts of creatine for long periods of time.[18] The administration of creatine in patients with progressive muscular dystrophy was followed by an increase in the creatinine output.[19] Thus we can see that there is an inherent defect in the metabolism of creatine and creatinine in this disease, manifest principally by diminished creatine tolerance, creatinuria, and diminished excretion of creatinine in patients not undergoing creatine tolerance studies.[20, 21]

Conclusion

Pseudohypertrophic muscular dystrophy is a progressive sex-linked Mendelian recessive or dominant disease affecting young males. The prognosis is poor in those affected at an early age, patients infrequently living past adolescence. Skeletal muscles of almost any part of the body may be involved. The gastrocnemius, soleus, gluteus, deltoid, supraspinatus and infraspinatus and facial muscles are involved most commonly. There is an inherent defect in the metabolism of creatine and creatinine in which one sees decreased excretion of creatinine, increased excretion of creatine and poor creatine tolerance. Creatine tolerance studies are indicated in this disease, for normal infants or children may also ex-

crete significant amounts of creatine in the urine. As a basis for the creatine tolerance test, 1.32 gm. of creatine hydrate (equivalent to 1 gm. of creatine) may be given to a patient on a standard diet low in creatine-precursor foodstuffs. Treatment of this disease has not been discussed as there is no treatment in use at the present time which has proved to be of sound value. Vitamin E, testosterone, glycine, ephedrine, etc., have all been used without success.

Summary

1. Pseudohypertrophic muscular dystrophy is essentially a disease of the peripheral skeletal muscles. It is heredofamilial in nature and affects primarily young males.

2. Defects in creatine-creatinine metabolism can be demonstrated consisting of diminished creatine tolerance, creatinuria and decreased excretion of creatinine in patients not undergoing creatine tolerance studies.

3. Creatine-creatinine studies indicate the amount of improperly functioning muscle mass and not the degree of destroyed muscle.

4. Treatment is unsatisfactory and is principally designed to prevent and combat lethal complications.

5. A case illustrating these salient features has been presented. The disease was traced back six generations in the patient's family, and was found to involve males in four of the six generations.

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EDITORIAL

THE ORAL EXAMINATION OF THE BOARD OF INTERNAL MEDICINE

An examination as a means of distinguishing between the well trained and capable and those whose actual ability is below a required standard, admittedly leaves a great deal to be desired. An opinion as to the competence of an individual when based on the result of an examination cannot compare in accuracy with an opinion gained in day to day contact with that individual as he meets the problems of his routine work. This is particularly true in medicine. The teachers and colleagues with whom a physician has been associated can judge his work with an accuracy that cannot be approximated by any type of examination, although, it must be admitted, such an appraisal is not invariably made without prejudice. In the case of physicians who wish to be certified to the public as specialists in internal medicine the opinion of the instructors under whom they have trained and the colleagues with whom they have worked would be the ideal evidence on which to base certification were it possible to obtain such an opinion, clearly and honestly expressed and without the possibility of favoritism and preferences based on personal likes and dislikes. Even if the Board were able to obtain uniformly unbiased appraisals of interns, residents and practicing physicians from the heads of their departments of medicine in medical schools and hospitals, the opprobrium and ill will that would result when honest but unfavorable ratings of individuals were rendered would be more than those who are charged with the duties of teaching and supervision should be asked to face. It has been necessary, therefore, for the American Board of Internal Medicine, to whom has been given the duty of certifying specialists in internal medicine, to utilize an impartial examination as the only practical means of carrying out its assignment.

A detailed description of the examinations now in use is presented in an article by Cecil J. Watson (J. A. M. A. **138**: 257–260, 1948). The reason for further discussion, directed to the Oral Examination, is that certain rumors and misapprehensions regarding this examination have been brought to the attention of the writer and a clarification appears to be indicated. The oral, the second part of the whole examination, is designed primarily as a more intimate and personal appraisal of the physician who, having passed the written test, may be considered to have demonstrated a factual knowledge of medicine, a familiarity with basic scientific concepts and recent advances, as well as an ability to give a correct solution to various clinical problems. In dealing with a candidate at the bedside the examiner asks himself, "Does this doctor show, by his approach to the patient, his skill in obtaining the history and completing the physical examination and by his overall evaluation of the situation presented, that he would be a man who could competently deal with such problems in the field of internal medicine

as might be referred to him by his colleagues or to solve which he might be called in consultation?" In many instances the clinical case to which the candidate is assigned is not such that the answer to the above question can be adequately determined and the examiner must, by further questioning, often on a variety of subjects, make up his mind as best he can. When, however, he has consulted with a second examiner, who has also questioned the same candidate, with a second patient as the basis of discussion, the combined opinion of the two examiners is probably as fair and accurate as it is possible and practical to obtain in an examination in which, unfortunately, a very large number of candidates must be interviewed. Were it not for the great demand for certification which has in the past year required, besides the two standard sessions, three extra examinations in various parts of the country, it would be possible to allow each candidate more time for the study of his patients and to give him a longer period with his examiners. This certainly would be very desirable could it be accomplished.

Despite the care in the selection of the members of the Board, and the earnest desire of each of them to make the examination as uniform, fair and without prejudice as is humanly possible, certain rumors and misapprehensions which deserve comment have been brought to the attention of the writer. One of these is to the effect that the chances of a particular candidate's passing the oral examination varies greatly with the individual examiners to whom he is assigned. This has even been exaggerated to the statement that certain examiners are "very tough" and have a failure rate as high as 90 per cent of the candidates examined while others are uniformly "easy." "The fact is that a careful study of the records of the individual members of the Board in the oral examinations made several years ago showed a variation of but 5 or 6 per cent in the proportion of candidates failed by each of them. There is every reason to believe that in the past five years it has not exceeded 10 per cent at the most."

It is quite true that there are some individual differences between examiners both in their approach to the candidate and their ability to put him at his ease and thus obtain evidence of his ability unobscured by the emotional tension which the situation often produces. Furthermore there is some difference in the importance attributed to various phases of the candidate's performance, in the judgment of different examiners. A good physical examination, for example, or a careful social and personal history, very possibly have more weight in the mind of one examiner than another. Such differences, however, are minimal and the members of the Board are constantly striving to make the examination as uniform as is humanly possible. A failure in this examination is not only disheartening to the candidate but it is always a disappointment to the examiner and the idea that any member of the Board could derive sadistic satisfaction from reporting the failure of a candidate is utterly false.

That the results of this examination, as of all others, entail an appreciable percentage of error may be readily admitted. It is generally recognized that certain individuals are clever in taking examinations though they may be otherwise of not more than average ability. Many a Phi Beta Kappa key adorns a man whose outstanding ability in preparation for and undergoing examinations masks a very mediocre knowledge of the subjects he has studied. In the same way physicians taking the oral examinations may occasionally succeed in producing a more favorable impression than is warranted by their real ability. The converse is true and perhaps even more regrettable. Many a thoroughly trained and able physician is so demoralized by the nervousness and anxiety entailed in taking the oral examination that his performance is utterly inadequate and quite out of line with his real ability. The examiners are alert at all times to recognize the "emotional block" which is evidenced by so many candidates but, nevertheless, a number of competent internists succeed, much against their will, in concealing their real ability and thus fail the examination. Every Board member is familiar with instances in which the failure of a candidate personally known to him to be a man of great ability seems almost incomprehensible.

There are many other questions regarding the broad subject of Board certification that merit general attention such as, for example, increasing tendency of hospitals to use certification as a requirement for appointment or promotion, thus asking the Board to take the responsibility for evaluations that these hospitals are themselves in much better position to make. These broader questions will not be considered here.

The opinions here expressed are those of the writer, but it is his belief that every member of the present Board is essentially in agreement with them. Definite improvements have been made and the Board is constantly striving for more. It is furthermore always open to suggestions and constructive criticism.

ALEX. M. BURGESS, M.D.

REVIEWS

Principles of Medical Statistics. (5th Ed). By A. Bradford Hill. 282 pages; 14 × 22 cm. Oxford University Press, New York. 1950. Price, $3.00.

There is a sort of rhythm in the literature of medicine. For example, the life cycle of a new therapy. The new method gains enthusiastic adherents who issue a series of laudatory reports. Then a reaction sets in, critics arise, controversy develops. Often a series of disparaging reports leads to the gradual abandonment of the therapy and a repetition of this cycle with some new candidate.

This periodic rise and fall applies not only to therapies but to technics and theories as well. Evidently this process is wasteful of the limited resources available for medical research. In this sense the rhythm is a pathological condition in the body of medical literature.

The question then arises: Is there any way of avoiding this waste? Are there methods which will provide some warning that an avenue for research is, in fact, a blind alley?

It is notable that this pathological rhythm is much less marked in such sciences as physics. In fact it appears that the more *quantitative* the science (the more that experiments, measurements, and numbers are used instead of *words*), the less distinct is the growth-decay rhythm. This has led to efforts to make medical research quantitative and hence to the development of "medical statistics." The use of numerical reasoning has not led to a complete cure, but some improvement has been evidenced.

Some doctors may feel that this "cure" is worse than the malady, others are deterred from trying the "cure" because they are afraid of the resulting arithmetic or algebra. For this latter group *Principles of Medical Statistics,* by Bradford Hill, which has now passed into its fifth edition is warmly recommended.

The author properly emphasizes that quantification is NOT accomplished by sprinkling a few rates, percentages, or other numbers in the text of a paper. It is necessary to have some grasp of statistical principles in order to draw valid conclusions from such numbers. Moreover numerical reasoning, like verbal reasoning, is subject to various pitfalls, some of which are not so obvious. It seems to me that any doctor who intends to submit papers for publication would do well to read carefully the several chapters on "common fallacies"—if only to save himself possible embarrassment.

Bradford Hill has made the material readable by providing extensive verbal explanations, choosing his examples from the medical literature, and giving any numerical procedures in great detail.

From a purely technical standpoint the book is a little dated. It fails to mention a number of useful technics (i.e., the analysis of sources of variation in measurements). Some of the discussions might be rephrased in terms of the work of Fisher, Neyman, and Wald. But as an introduction to medical statistics for the *medical profession* this book retains its position at the top of the list.

I. B.

Management of Celiac Disease. By Sidney Valentine Hass, M.D., and Merrill Patterson Hass, M.D. 188 pages; 24 × 16 cm. J. B. Lippincott Co., Philadelphia. 1951. Price, $5.00.

Although celiac disease is principally a disease of infancy and early childhood, the subject also concerns the adult internist in that the disease sometimes persists into adolescence or even early adult life, especially if poorly managed. Even if overcome

earlier, the disease may leave some sequelae such as stunting of stature. The disease is quite similar to what the internist calls non-tropical sprue.

The authors are to be commended for emphasizing the probable importance of complex carbohydrates rather than fats in the pathogenesis and dietary management. The discussion, however, seems to overlook certain items which would tend to support the distinction between celiac disease and cystic fibrosis of the pancreas.

Most authorities will firmly disagree with the reluctance of the authors to distinguish between celiac disease and cystic fibrosis of the pancreas. This lack of differentiation seems particularly unfortunate in the section on pathology.

An excellent bibliography is provided.

G. G.

A Textbook of Psychiatry for Students and Practitioners. 7th Ed. By Sir David Henderson and the late R. D. Gillespie. 740 pages; 22.5 × 14.5 cm. Oxford University Press, New York 11, N. Y. 1950. Price, $7.75.

This *Textbook of Psychiatry,* now in its seventh edition, remains one of the classic texts on the subject. Over 700 pages cover most aspects of psychiatry including some historical background, classification, descriptions of the psychoses, the psychoneuroses and the psychopathic states. Equally well done are chapters on mental deficiency, the organ reaction types and epilepsy. One entire chapter is devoted to child psychiatry. The book attempts to provide separate sections, usually very brief on etiology, psychopathology, on occasion, physiology, and on treatment. The author's orientation is typically eclectic being chiefly the psychobiologic approach of Dr. Adolph Myer. Freudian psychoanalytic theory is made mention of frequently in discussion of psychopathology but is usually qualified by stating its applicability in only a minority of cases. Some quotations of Freudian theory have long since been modified by a majority of those in the psychoanalytic school.

The authors draw richly on the literature and while an excellent attempt has been made to summarize and condense, some of the detailed classifications would tend to bog down one's efforts for rather quick reference or information regarding some diagnosis or syndrome. This is partially compensated for by illustrative case material. Over 90 such cases are presented which high light in interesting fashion the descriptive material in the text.

For more specialized interest chapters are included on special methods of treatment which present in some detail technics of insulin, electric shock and metrazol treatment. Included here too is a section on surgical treatment of mental disorders, which has been brought up to date from the previous edition (1944) by further discussion of results of leucotomy and a short discussion of topectomy. A chapter on war neuroses and psychoses has also been made more inclusive than the chapter in the preceding edition by the addition of more material on the traumatic neuroses and prevention. Little else has been revised except for the chapter on etiology in which statistics on the incidence of various mental conditions has been brought up to date.

In the sections on treatment of various conditions one sees some differences with that used more customarily in American medical practice. For example, the use of bromides in epilepsy as the mainstay of therapy. Little has been included of the newer anti-convulsants. In the treatment of acute alcoholic conditions none of the stress we place on hydration and establishing electrolyte balance has been emphasized. A practice not in much favor in this country is the giving of sugar to children for so-called "glycopenic" states of which night terrors was given as an example.

However, taken as a whole the book is carefully done and remains as a definite source of general information and reference for psychiatric theory and practice.

H. W. N.

Symposium on Steroids in Experimental and Clinical Practice. Edited by ABRAHAM WHITE for the Committee on Arrangements. 415 pages; 15.5 × 23.5 cm. The Blakiston Co., Philadelphia 5, Pa. 1951. Price, $7.50.

The First Annual Steroid Conference was held in Cuernavaca, Mexico, January 1951. The present volume consists of the papers presented there and the discussions following them. The papers are progress reports on evaluation of the physiological studies and therapeutic trials of various steroids, principally pregnenolone. The conflicting evidence presented leaves much doubt as to whether pregnenolone is of any value in rheumatoid arthritis, the condition most concerned in these studies. The discussions emphasize the difficulty in and necessity for rigorous scientific control of clinical studies attempting such evaluation. According to one report, which deserves further substantiation, pregnenolone has a spermatogenic action useful in treatment of sterility. Progesterone was shown to cause retrogressive changes in carcinoma of the cervix, but not to a degree which would justify routine clinical use at present.

G. G.

Management of Peripheral Arterial Diseases. By SAUL S. SAMUELS, A.M., M.D., Chief of the Department of Arterial Diseases, Stuyvesant Polyclinic Hospital, New York; Consulting Vascular Surgeon, Long Beach Hospital, Long Beach, New York; Director and Attending Angiologist, Brooklyn Hebrew Home and Hospital for Aged, Brooklyn, New York; Fellow in Surgery, New York Academy of Medicine; Member of Committee on Surgery, New York Diabetes Association; Editor-in-Chief, *Angiology;* President, Angiology Research Foundation. 345 pages. 14.5 × 22.5 cm. Oxford University Press, New York. 1950. Price, $7.50.

This text minutely discusses all of the peripheral arterial diseases. The author has presented each separate disorder in a very orderly and easily understood manner.

Clear and concise sections on the various phases of diagnosis, symptoms, treatment, etc. are each followed by a complete bibliography. There has been a liberal use of photographs.

The great variety of case presentations indicates the author's wide range of experience with vascular problems. The sections on treatment are very detailed, and little doubt is left in the reader's mind of the author's opinion of smoking in the presence of arterial disease.

The importance of Oscillometry in the diagnosis is pointed out, and in Chapter IV the author describes a type of pulsimeter which he has developed.

W. D. L.

BOOKS RECEIVED

Books received during September are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Application of Scientific Methods to Industrial and Service Medicine (Proceedings of a Conference held from March 29th to March 31st, 1950). 112 pages; 24.5 × 15 cm. (paper-bound). 1951. His Majesty's Stationery Office, London. Price, 3 shillings net.

Bacterial and Virus Diseases: Antisera, Toxoids, Vaccines and Tuberculins in Prophylaxis and Treatment. 2nd ed. By H. J. PARISH, M.D., F.R.C.P.E., D.P.H., Clinical Research Director, Wellcome Foundation, Ltd., etc. 204 pages; 19 × 12.5 cm. 1951. The Williams and Wilkins Company, Baltimore. Price, $2.50.

From Dugout to Hilltop. By MARGARET R. STEWART, M.D. 233 pages; 22.5 × 14 cm. 1951. Murray & Gee, Inc., Culver City, California. Price, $3.75.

Maternal Nutrition and Child Health: An Interpretative Review—Bulletin of the National Research Council, Number 123, November, 1950. By KIRSTEN UTHEIM TOVERUD, GENEVIEVE STEARNS and ICIE G. MACY. 174 pages; 25.5 × 17.5 cm. (paper-bound). 1951. The National Research Council, National Academy of Sciences, Washington, D. C. Price, $2.00.

The 1951 Year Book of Medicine (May, 1950-May, 1951). Edited by PAUL B. BEESON, M.D., J. BURNS AMBERSON, M.D., WILLIAM B. CASTLE, M.D., S.M. (Hon.) Yale, M.D. (Hon.) Utrecht, TINSLEY R. HARRISON, M.D., and GEORGE B. EUSTERMAN, M.D. 696 pages; 20 × 13.5 cm. 1951. The Year Book Publishers, Incorporated, Chicago. Price, $5.00.

Ophthalmology. By ARNO E. TOWN, M.D., Professor of Ophthalmology, The Jefferson Medical College of Philadelphia. 511 pages; 24 × 15.5 cm. 1951. Lea & Febiger, Philadelphia. Price, $10.00.

Renal Pelvis and Ureter. By PETER A. NARATH, M.D., F.I.C.S., Adjunct Professor of Urology, New York Polyclinic Medical School and Hospital. 429 pages; 26 × 17.5 cm. 1951. Grune & Stratton, New York. Price, $12.50.

Studies of Undernutrition, Wuppertal 1946–9—Medical Research Council Special Report Series No. 275. By Members of the Department of Experimental Medicine, Cambridge, and Associated Workers. 434 pages; 24.5 × 15 cm. (paper-bound). 1951. His Majesty's Stationery Office, London. Price, 12s. 6d. net.

Syphilis. By RICHARD S. WEISS, M.D., Professor Emeritus of Clinical Dermatology, School of Medicine, Washington University, etc.; and HERBERT L. JOSEPH, M.D., Consultant in Dermatology and Syphilology, U. S. Air Force Base, Travis Air Force Base, California, etc. 180 pages; 23.5 × 15.5 cm. 1951. Thomas Nelson & Sons, New York. Price, $5.00.

A Textbook of Clinical Neurology. 3d ed. By J. M. NIELSEN, B.S., M.D., F.A.C.P., Clinical Professor of Neurology and Psychiatry, University of Southern California, etc. 709 pages; 26.5 × 18 cm. 1951. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $10.00.

A Textbook of Medicine. Edited by E. NOBLE CHAMBERLAIN. 962 pages; 23.5 × 16 cm. 1951. The Williams and Wilkins Company, Baltimore. Price, $10.00.

ERRATUM

July, 1951, "Studies in Disorders of Muscle. IV. The Clinical Manifestations and Inheritance of Childhood Progressive Muscular Dystrophy" by Frank H. Tyler and F. E. Stephens, page 181, the first line below the table should read, "349,525 normal females, 1 carrier female, 349,525 normal males and 1 dystrophic male."

COLLEGE NEWS NOTES

A.C.P. Postgraduate Courses

The Postgraduate Courses arranged by the American College of Physicians during the Autumn of 1951 have been universally successful and have attracted a large registration. The only remaining courses on the autumn schedule are as follows:

Course No. 8, CARDIOVASCULAR DISEASES. University of Texas Medical Branch, Galveston, Tex.; George R. Herrmann, M.D., F.A.C.P., Director; December 10–15, 1951.

Course No. 9, PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE. University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Julius H. Comroe, Jr., M.D., F.A.C.P., Director; December 10–15, 1951.

The schedule of Postgraduate Courses for the Winter and Spring of 1952 will be announced in an early issue of this journal, following the meeting of the Advisory Committee on Postgraduate Courses during November.

A.C.P. Regional Meetings

During the month of October and early November, Regional Meetings of the College were held under the direction of the respective Governors for Montana-Wyoming, at Butte, October 5–6; Pacific Northwest, at Seattle, October 5–6; Midwest, at Columbus, Ohio, October 13; New England, at Portland, Maine, October 20; Kentucky, at Louisville, October 27; and Northern California, at San Francisco, November 2. At the time of the preparation of this report, full data about attendance, etc., are not yet available but the programs have been universally excellent with an opportunity for many of the younger members to participate. The College is fully cognizant of the excellent services rendered by its various Governors and the various Fellows and Associates who have assisted on the various committees and participated in the programs.

The following Regional Meetings are definitely scheduled and others are in process of organization:

SOUTHEASTERN REGIONAL MEETING (Alabama, Florida, Georgia, South Carolina and Cuba)	Jacksonville, Fla.	November 2–3, 1951
NEW JERSEY REGIONAL MEETING	Newark	November 7, 1951
MIDSOUTH REGIONAL MEETING (Louisiana, Tennessee, Texas, Mississippi, Arkansas, Oklahoma)	New Orleans, La.	February 15–16, 1952
PUERTO RICO REGIONAL MEETING	San Juan	February 17, 1952
KANSAS REGIONAL MEETING	Omaha	March 21, 1952

The "Tele-clinic" motion picture film of the 32nd Annual Session of the American College of Physicians, depicting the highlights of the meeting, has been shown at numerous Regional Meetings and has been received with much appreciation and praise not only by those who were not in attendance at the St. Louis Session but also

by those who were present. The film requires 35 minutes for running, is 16 mm., sound. It covers the highlights of the opening of the Session, the Convocation and gives 5 of the most important presentations in abstract by the speakers themselves. Several copies of the film have been made and are available to groups of physicians anywhere in the United States. Consult the News Notes Section of the September, 1951 issue of this journal for various distribution points, or write the Executive Secretary of the American College of Physicians for details.

33rd Annual Session, Cleveland, April 21–25, 1952

Arrangements for the 1952 Annual Session of the College are rapidly taking form and the program is being prepared. The President of the College, Dr. Maurice C. Pincoffs, University Hospital, Baltimore 1, Md., is in charge of the program of General Sessions and Morning Lectures. Dr. Roy W. Scott, 3395 Scranton Rd., Cleveland 9, Ohio, is the General Chairman of the Session and is supervising the program of Clinics, Panel Discussions and local arrangements. The program of colored televised clinics will be continued.

The Cleveland Municipal Auditorium will be utilized for all sessions and the Technical Exhibit.

Hotel Reservations: The College will designate a complete list of official hotels and a Housing Bureau is being set up in Cleveland to handle all hotel reservations. In view of the fact that the American Board of Internal Medicine will be giving oral examinations in Cleveland during the preceding week and the American Heart Association will hold its Annual Meeting in Cleveland, also during the preceding week, there is being devised a hotel reservation form for the accommodation of all members who will be in Cleveland either or both of the two weeks. By using these special forms they can be assured of not having to move from one hotel to another after the first week. These special reservation forms should be ready for distribution during December.

Arkansas-Oklahoma Regional Meeting Held at Hot Springs

The 5th Annual Regional Meeting of the College for Arkansas and Oklahoma was held at Hot Springs National Park, September 29, 1951, under the Governorships of Dr. A. A. Blair, of Arkansas, and Dr. Wann Langston, of Oklahoma. Dr. Oliver C. Melson, former Governor for Arkansas, was Chairman of the Program Committee, and Dr. Driver Rowland of Hot Springs was Chairman of Arrangements. The program was especially well received, being of a nature that appealed to the members in the area as testified to by their constant attendance throughout the meeting. Eighty per cent of the members in Arkansas and 38 per cent of the members in Oklahoma were registered. The total registration indicates 46 Fellows, 16 Associates, 43 Non-members, making a grand total of 105. A banquet was held in the evening at the Arlington Hotel. Dr. Cyrus C. Sturgis, a member of the Board of Regents of the College, and Professor of Internal Medicine at the University of Michigan, gave an address on the Research and Latin-American Fellowship Programs of the College. Mr. E. R. Loveland, Executive Secretary of the College, spoke on the spirit of the American College of Physicians and showed the tele-clinic film which depicted the highlights of the last Annual Session of the College in St. Louis. Members found this film extremely interesting and several physicians who were present are making arrangements to borrow the film for showing to other groups of physicians.

Gift to the College Library of Publications by Members

Dr. William S. Reveno, F.A.C.P., Detroit, Mich., has presented the College Library of Publications by Members with an autographed copy of his book, "711 Medical Maxims."

The College Library of Publications by Members is maintained at College headquarters. Members frequently present copies of their books to the College and thus the library has become a living memorial to the member-authors.

University of Oklahoma School of Medicine Offers Postgraduate Courses

The University of Oklahoma School of Medicine has recently announced its Postgraduate Schedule of Courses for the Autumn of 1951 and the Winter and Spring of 1952. In addition to courses in General Surgery, Surgical Pathology and Surgical Technic, it includes the following courses:

Cardiology: November 15, 16 and 17, 1951; fee $15.00.
General Pediatrics: December 12, 13 and 14, 1951; fee $15.00.
Laboratory Examinations in Clinical Diagnosis: January 28-February 2, 1952; fee $60.00.
Practical Psychiatry; February 25 and 26, 1952; fee $10.00.
Electrocardiography: March 3–8, 1952; fee $60.00.
X-ray Diagnosis: May 2 and 3, 1952; fee $10.00.

For registration blank and course details address the Office of Postgraduate Instruction, University of Oklahoma School of Medicine, 800 N.E. 13th St., Oklahoma City, Okla.

Postgraduate Courses by Kings County Medical Society and State University College of Medicine at New York

The Medical Society of the County of Kings and the State University College of Medicine of New York City recently announced its fall program of postgraduate courses, designed primarily for the general practitioner, and not intended to train a physician to become a specialist. The Joint Committee on Postgraduate Education is headed by Dr. Jean A. Curran, M.D., F.A.C.P., Dean of the State University College of Medicine. The sessions are so arranged that they afford an opportunity for the busy practitioner to engage in postgraduate study without giving up his practice. Therefore, the courses are given one, two or three different hours on different days of the week. The Postgraduate Bulletin and application forms may be obtained through the Joint Committee on Postgraduate Education, Medical Society Bldg., 1313 Bedford Ave., Brooklyn 16, N. Y.

The New York Academy of Medicine Postgraduate Lectures

The New York Academy of Medicine, among many other activities, conducts a series of Friday afternoon postgraduate lectures devoted to recent advances in the particular subject under discussion, the lectures given by well known authorities in the field. This program extends from November 2, 1951, to April 18, 1952, and physicians in the New York area may obtain the programs from the Academy at 2 E. 103rd St., New York 29, N. Y.

Applications are being received for a two-year Fellowship in Medicine at Cornell-New York Hospital. The recipient will work with Drs. Harold G. Wolff, William H. Dunn and Stewart Wolf, spending one-half the time in experimental work and the other half in obtaining clinical experience with patients with stress disorders. The fellowship will begin in July, 1952.

Award for Outstanding Research in the Field of Infertility

The American Society for the Study of Sterility announces the opening of the 1952 contest for the most outstanding contribution to the subject of infertility and sterility. The winner will receive a cash award of one thousand dollars, and the essay will appear on the program of the 1952 meeting of the Society. Essays submitted in this competition must be received not later than March 1, 1952. For full particulars concerning requirements of this competition, address The American Society for the Study of Sterility, 20 Magnolia Terrace, Springfield, Mass.

American Board of Pediatrics Examinations

The written examination scheduled by the American Board of Pediatrics, under local monitors, will be held on Friday, January 11, 1952. This will be the only written examination which will be given during 1952.

The oral examinations, scheduled for 1952, are as follows:

New York, N. Y.—February 1, 2, and 3, 1952,
St. Louis, Mo.—April, 1952,
Washington, D. C.—May 3, 4, and 5, 1952,
San Francisco, Calif.—late June, 1952,
Chicago, Ill.—October, 1952,
Boston, Mass.—late November, 1952.

Public Health and Clinical Physicians Needed in New York State

The New York State Department of Health announces openings for public health and clinical physicians in the fields of tuberculosis control, local health administration, communicable disease control and maternal and child health. No written or oral examinations will be held for these positions, but candidates will be rated on their past education and professional experience in relation to the minimum qualifications for the positions. Beginning salaries range from $6,991.00 to $8,594.00 per annum, depending upon the position in question. Application blanks and further information may be obtained through the Examinations Division, Department of Civil Service, 39 Columbia St., Albany 1, N. Y.

The 16th Annual Meeting of the Mississippi Valley Medical Society was held in Peoria, Ill., September 19–21. Among the speakers on the scientific program were eight Fellows of the College: Dr. George E. Wakerlin, Chicago, Ill., "The Kidneys and Hypertension"; Dr. Fred M. F. Meixner, Peoria, "Routine Chest Roentgenograms in General Hospital Admissions"; Dr. O. C. E. Hansen-Pruss, Durham, N. C., "Treatment of Asthma and the Postural Syndrome"; Dr. Robert N. Keeton, Chicago, Ill., Moderator, Noon Round Table Luncheon; Dr. Chauncey C. Maher, Chicago, Ill.,

"Diagnosis and Treatment of Cardiac Emergencies" and "What's New in Cardiology"; Dr. Daniel L. Sexton, St. Louis, Mo., "What's New in Endocrinology"; Dr. Willard O. Thompson, Moderator of Panel: "What's New in Medicine and Surgery"; Dr. Edmund F. Foley, Chicago, Ill., "Common Causes of Jaundice with Special Reference to Differential Diagnosis" and "What's New in Diseases of the Liver."

Dr. Oliver C. Melson, F.A.C.P., Little Rock, Ark., is President of the Arkansas State Heart Association.

Dr. Lee D. Cady, F.A.C.P., Manager of the Veterans Administration Hospital, Houston, Tex., was recently elected a member of the American College of Hospital Administrators.

Dr. LeMoyne Copeland Kelly, F.A.C.P., New Haven, President of the State of Connecticut Arthritis Society, and Dr. Charles Slocumb, Mayo Clinic, Rochester, Minn., President of the American Rheumatism Association, have returned from the Second European Congress on Rheumatic Diseases held in Barcelona, Spain. Dr. Kelly, who went as an official delegate of the United States, read a paper on "The Modern Day Treatment of Arthritis of the Spine." Dr. Slocumb, as guest of honor, spoke on "Non-articular Rheumatism." This world-wide conference was attended by physicians from 52 countries.

Dr. Thomas Hodge McGavack, F.A.C.P., Professor of Clinical Medicine, New York Medical College, attended the Second European Congress of Rheumatology, Barcelona, Spain, September 24 to 27 and presented a paper on "The Influence of Pregnenolone upon Arthritis and Certain 'Collagen' Diseases."

Dr. Burgess Lee Gordon, F.A.C.P., President of The Woman's Medical College of Pennsylvania, was tendered a testimonial dinner at the Hotel Barclay, Philadelphia, on October 18.

Dr. Harold E. Himwich, F.A.C.P., former Chief of Clinical Research at the Army Chemical Center, Md., has taken an appointment with the Galesburg (Ill.) State Research Hospital.

Dr. Richard L. Harris, F.A.C.P., Montrose, New York, was appointed Assistant Professor of Clinical Psychiatry, Cornell University Medical College, New York, New York.

Dr. Leon L. Rackow (Associate), Montrose, New York, was appointed Instructor in Psychiatry, Cornell University Medical College, New York, New York.

Dr. William A. Sodeman, F.A.C.P., Chairman of the Department of Tropical Medicine and Public Health of Tulane University of Louisiana School of Medicine, has been awarded a Fulbright lectureship grant at the Calcutta, India, School of Tropical Medicine, teaching both clinical and tropical medicine. Dr. Sodeman will remain at the Calcutta school for one year.

Among the guest speakers at the Annual Conference of the Kansas City Southwest Clinical Society held October 1–4 in Kansas City, were Dr. Edward F. Bland, F.A.C.P., Boston, Mass., "Course and Complications of Rheumatic Heart Disease, with Special Reference to Management," and Dr. H. Marvin Pollard, F.A.C.P., Ann Arbor, Mich., "Modern Therapy for Gastroduodenal Ulcer."

Dr. Walter H. Baer, F.A.C.P., Superintendent of the Peoria (Ill.) State Hospital, was recently appointed Acting Deputy Director of the Illinois Department of Public Welfare.

Dr. Lewis J. Moorman, F.A.C.P., Oklahoma City, Secretary of the Oklahoma State Medical Association and Editor of the *Journal of the Oklahoma State Medical Association*, was elected President-Elect of the American Medical Writers Association at the Eighth Annual Meeting, held in Peoria, Ill., on September 19. At the same time, Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., was elected Secretary-Treasurer, and Dr. Lee D. VanAntwerp, F.A.C.P., Chicago, Ill., was elected Editor. Among those elected to the Board of Directors was Dr. Theodore R. VanDellen, F.A.C.P., Chicago, Ill.

After a year's leave of absence with the World Health Organization of the United Nations, Dr. E. Herndon Hudson, F.A.C.P., has resumed his position as Director of the Ohio University Health Service. During his leave, Dr. Hudson organized a bejel syphilis project in Iraq, with headquarters in Baghdad, with six months of field work during which he and his team accumulated much scientific information.

The 48th Annual Meeting of the Wyoming State Medical Society was held in Rock Springs, September 27–29. Among the guest speakers were Dr. Walter J. Freeman, F.A.C.P., Washington, D. C., whose topic was "Psychosurgery," and Dr. J. Earle Estes (Associate), Minneapolis, Minn., who spoke on "Occlusive Arterial Diseases of the Extremities."

Dr. Travis Winsor, F.A.C.P., Los Angeles, Calif., was one of the speakers at the 3rd Annual Symposium of the Washington State Heart Association in cooperation with the Washington State Department of Health on "Diagnosis and Therapy of Peripheral-Vascular Diseases," which was held in Seattle, October 19–20.

Dr. John E. Gordon, F.A.C.P., Boston, Mass., is one of the members of a medical teaching mission composed of fourteen specialists from six different countries, which left recently from Geneva for Israel and Iran under the sponsorship of the World Health Organization and the Unitarian Service Committee.

Among the speakers at the Annual Meeting of the Southwestern Medical Association, which was held in El Paso, Tex., October 18–20, was Dr. Elmer C. Bartels, F.A.C.P., Boston, Mass., whose topic was "Present-day Treatment of Hyperthyroidism."

The University of Michigan Medical School has announced the promotion of Dr. Herman M. Pollard, F.A.C.P., to the rank of Professor of Internal Medicine.

Dr. William Henry Sebrell, Jr., F.A.C.P., Bethesda, Md., Director of the National Institutes of Health, U. S. Public Health Service, has been elected to the Board of Directors of the National Society for Medical Research.

Four Fellows of the College were among the guest speakers at the Postgraduate Medical Assembly of the Nashville Academy of Medicine, which was held October 3-5. They were: Dr. Edgar Hull, New Orleans, College Governor for Louisiana, "Cardiac Emergencies and Their Management"; Dr. Warren E. Quillian, Coral Gables, Fla., "Pyurias in Childhood"; Dr. A. McGehee Harvey, Baltimore, Md., "The Current Status of ACTH and Cortisone in Medical Practice"; and Dr. Tinsley R. Harrison, Birmingham, Ala., "Practical Aspects of Palpitation."

Dr. Jay A. Myers, F.A.C.P., Minneapolis, Minn., and Dr. Burgess L. Gordon, F.A.C.P., Philadelphia, Pa., were among the guest speakers included on the program of the Wisconsin chapter of the American College of Chest Physicians, which was held on September 30. Dr. Myers' subject was "Primary Tuberculosis in Adults," and Dr. Gordon spoke on "Physiological Considerations in the Diagnosis and Management of Chronic Pulmonary Diseases."

The Association of Life Insurance Medical Directors of America met in New York, N. Y., October 11–12, under the presidency of Dr. Lauritz S. Ylvisaker, F.A.C.P., Philadelphia, Pa. Among the guest speakers were Dr. Philip S. Hench, F.A.C.P., Rochester, Minn., "Cortisone and ACTH"; Dr. Francis R. Dieuaide, F.A.C.P., New York, N. Y., "Progress in Cardiovascular Research"; Dr. Thomas M. Durant, F.A.C.P., Philadelphia, Pa., "Dietary Factors in Arteriosclerosis," and Dr. Howard M. McCue, Jr. (Associate), Richmond, Va., "Control of Rheumatic Heart Disease."

Dr. Arthur J. Revell, F.A.C.P., has retired as Chief Medical Officer of the Veterans Administration Office, at Topeka, Kansas, and has accepted an appointment as Clinical Director of the East Texas Tuberculosis Sanatorium at Tyler, Tex.

Dr. Blair Holcomb, F.A.C.P., Portland, Oregon, was installed as President of the Oregon State Medical Association, at Portland, on October 9, 1951.

OBITUARIES

DR. WILLARD JOSEPH DENNO

Dr. Willard Joseph Denno, F.A.C.P., retired General Medical Director of the Standard Oil Company (N. J.), died at his home in New York City on August 29, 1951.

Dr. Denno was born in Castleton, Vt., on August 25, 1878, the son of Gustavus E. and Della Hoskins Denno. He was graduated from the Castleton Normal School and taught school in Vermont for several years before matriculating at Yale University in 1903. He received his medical degree in 1906 from the College of Physicians and Surgeons at Columbia.

He served an internship of two years at the General Memorial Hospital in New York and for the following three years was associated with the New York City Health Department. During this period he was an attending physician in the Department's tuberculosis clinics and later became assistant to the director of the Division of Tuberculosis.

Dr. Denno also served as secretary of the New York State Department of Health and studied under Dr. William H. Park and his associates for the degree of Doctor of Public Health, which he received in 1916.

Two years later he accepted a position with the Standard Oil Company (N. J.) to organize its medical department. He remained as General Medical Director of that company for 27 years. Under his guidance the Medical Department expanded to a world-wide organization. At the time of his retirement, December 31, 1945, the original medical department and those of affiliated companies were composed of more than 150 physicians, 1500 nurses and attendants, and 11 hospitals, and represented the largest medical organization of its type in the world.

His greatest contribution to medicine in industry was his broad vision in foreseeing the requirements of a medical department in order for it to assume its proper rôle in the affairs of a modern-day business enterprise. Only such an individual, whose outstanding characteristics were those of leadership and organization, could have made this tremendous progress in this relatively short time.

Dr. Denno was a Fellow of the American College of Physicians (since 1935), the American Public Health Association and the American Medical Association. He was a member of the Medical Society of the State of New York, the New York Academy of Medicine and the American Association for the Advancement of Science. He was the author of many articles dealing with medicine in industry and co-author of "The Health Officer," published in 1919.

Dr. Denno's career has been unequalled in his field and while the medical profession has lost a great leader and scholar, the greatest loss will be felt by those members of the medical organization which he founded.

K. R. Fourcher, M.D., F.A.C.P.

DR. CECIL CLINTON BIRCHARD

Cecil Clinton Birchard, M.B. (1911), M.D. (1928) (Toronto), F.R.C.P. (London), F.R.C.P.(C.), F.A.C.P., died at the Toronto General Hospital on July 30, 1951, after a short illness that developed while he was on his holidays.

Born in Ontario, he received his preliminary education in that province, and graduated from the University of Toronto in 1911 with honors in Medicine.

After graduation, Dr. Birchard joined the staff of the Montreal General Hospital as an interne on the Medical Service, the first step in a lifetime association with this hospital. In 1950, he was appointed Consulting Physician to the Hospital on the

occasion of his retirement from the active attending staff in which he held the rank of Attending Physician. He was also Chairman of the Medical Board and Secretary of the Corporation.

Always a keen student and teacher, Dr. Birchard was especially interested in the circulatory system and was one of the pioneers of electrocardiography in Montreal. He organized and was appointed Director of the Department of Electrocardiography at the Montreal General Hospital. As a teacher he rose through the ranks and at the time of his retirement was Associate Professor of Medicine on the Medical Faculty of McGill.

In 1915, he was appointed Medical Officer to the Sun Life Assurance Company of Canada, and soon after was raised to Chief Medical Officer, which position he occupied actively until the time of his death.

During the first World War, he served as a Captain in the Canadian Army Medical Corps, from 1916 to 1919, resuming his activities in Montreal on his return from service overseas.

Dr. Birchard was a Fellow of the Royal College of Physicians of London, a charter Fellow of the Royal College of Physicians of Canada, and a Fellow of the American College of Physicians. He was also a member of the Canadian Medical Association and of the Montreal Medico-Chirurgical Society, of which he was Vice President at the time of his death. He was a founder and first President of the Canadian Heart Association, of which he was a Councillor, and past President of the Canadian Life Insurance Medical Directors Association.

A physician with a flair for mathematics, he was a man of wide knowledge and great enthusiasm which stood him in good stead in considering the problems with which he was presented. His passing is a loss to Canadian Medicine.

WALTER DE M. SCRIVER, M.D., F.A.C.P.,
Governor for Quebec

DR. JACOB JONES COONS

Dr. Jacob Jones Coons, Sc.D., F.A.C.P., one of Ohio's pioneer medical leaders and educators, died on July 25, 1951, aged 77 years. Dr. Coons received his B.S. degree at Ohio Wesleyan University in 1898, and was awarded the Honorary Doctor of Science degree by his alma mater in 1921.

Graduating from the Johns Hopkins School of Medicine in 1902, Dr. Coons served as an assistant to the great teacher-clinician, Sir William Osler, at that institution during the following year. He was assistant resident surgeon at the Kensington Hospital, Philadelphia, Pennsylvania, during 1903–04. He continued his postgraduate studies at the University of Vienna in 1910.

Returning to Columbus, Ohio, in 1904, he established the first clinical diagnostic and pathologic laboratory in central Ohio, and thus set the pattern for all subsequent laboratories devoted to this important adjunct to exact diagnosis and modern specific therapy in this area.

A diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians since 1927, he became an Assistant Professor of Medicine at Ohio State University in 1914, and full Professor in 1924. He was retired as Clinical Professor of Medicine Emeritus in 1936. Dr. Coons served in numerous capacities on the staffs of Mt. Carmel, Grant and White Cross Hospitals, as well as the University Hospital during the entire active years of his medical career.

Dr. Coons was beloved by many generations of medical students and he held the respect and affection of all of his medical confreres. He was an active participant

in all activities of the American College of Physicians from 1927 until 9 years ago when he retired from active medical practice.

He is survived by his wife and married daughter.

CHARLES A. DOAN, M.D., F.A.C.P.,
Governor for Ohio

DR. FREDERICK OLAF FREDRICKSON

Frederick Olaf Fredrickson, M.D., F.A.C.P., was born in Chicago, Ill., November 8, 1874, and died on July 6, 1951, in Chicago, of pneumonia. He is survived by a niece, Miss Lillian Ekren, of Chicago. His wife, Nora C. Christopher, whom he married in Chicago on June 25, 1910, died in 1940. He and his wife were a devoted couple and her death was a severe blow to him.

Dr. Fredrickson graduated from Rush Medical College in 1908 and after interning at St. Joseph's Hospital, Chicago, he became Assistant in Medicine at Rush Medical College and advanced through the various grades to the post of Assistant Clinical Professor of Medicine. At the time of his death, Dr. Fredrickson was Assistant Professor of Medicine, Emeritus, at the University of Illinois College of Medicine. He was also an active member of the attending staff of Ravenswood Hospital in Chicago. For a number of years he conducted a clinic on gastrointestinal diseases for a small group of students in the Central Free Dispensary. He was always lively and enthusiastic in his teaching and he was appreciated by the undergraduate students in clinical medicine.

During the Mexican Border incident in 1916, Dr. Fredrickson served as a Captain in the Medical Corps of the Illinois National Guard. When World War I broke out he was promoted to Major and organized and commanded Field Hospital No. 130 of the 33rd Division. He was in active service overseas and in the Army of Occupation until 1919.

Dr. Fredrickson was a Fellow of the American Medical Association and a member of his county and state medical societies. He was a Past President of the Illinois State Medical Society. In 1931 he became a Fellow of the American College of Physicians, and a Life Member in 1934. He was also a Diplomate of the American Board of Internal Medicine and a member of the Chicago Society of Internal Medicine. Dr. Fredrickson practiced Internal Medicine in Chicago during all of his professional life.

He was extremely modest, laughed easily and had a keen sense of humor. He was an able organizer, a good leader and always worked well on a team. Outside of medicine, he was always a good citizen, and was active in the American Legion and in the Masonic Fraternity (32nd degree, Shriner).

Dr. Fredrickson had a fine tenor voice and all of his life enjoyed singing. In Chicago he sang for many years in several choral societies. He leaves a host of friends and devoted patients. The College has lost a faithful member.

HOWARD WAKEFIELD, M.D., F.A.C.P.,
Governor for Northern Illinois